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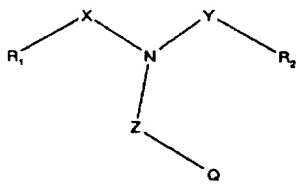
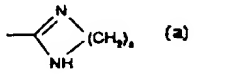
(54) Title: ANTIRETROVIRAL BASES

(57) Abstract

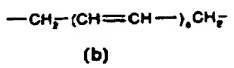
The invention relates to the use of a compound of formula (I), wherein R_1 and R_2 are independently amino, N-alkylamino, N,N-dialkylamino, cycloalkylamino, amidino, N-lower alkylamidino, N,N-di-lower alkylamidino, guanidino, N-lower alkylguanidino, N,N-di-lower alkylguanidino or (a); X and Y are independently selected from the group consisting of $-(CH_2)_b-$, (b), (c) and $-(CH_2)_g$-Cycloalkylen-$(CH_2)_h-$; Z is, independently of X and Y, $-(CH_2)_b-$, (d) or (e), wherein R is hydrogen or lower alkyl; Q is aryl, arylcarbonyl, arylaminocarbonyl, heterocyclyl, heterocyclylcarbonyl or heterocyclylaminocarbonyl, aryl or heterocyclyl whenever mentioned containing 2 or more annelated rings, a is 2 to 4, b is 2-7, c, d, e and f is 1 to 3, respectively, g and h is 0 to 3, respectively, i is 2 to 7 and k is 1 to 3, with the proviso that Q is arylcarbonyl, arylaminocarbonyl, heterocyclylcarbonyl or heterocyclylaminocarbonyl only if Z is a bivalent radical of formula (f) or (g); a tautomer thereof, or a salt thereof, as antiretroviral therapeutic (also for prophylaxis) inhibiting the interaction of transcriptional regulators with retroviral response elements.



(I)



(a)



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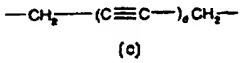

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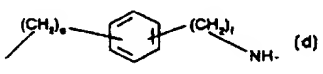

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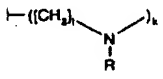

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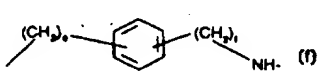

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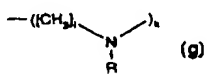

(g)

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Antiretroviral Bases

The present invention relates to a novel use of compounds, as such or in the form of pharmaceutical compositions, as antiretroviral therapeutics (also for prophylaxis) inhibiting the interaction of transcriptional regulators with retroviral response elements, to processes for the manufacture of pharmaceutical compositions for the novel intended use, to pharmaceutical compositions comprising the compounds and to novel intermediates and/or to a method of treatment comprising administering such a compound; the invention also relates to novel compounds of that type, to those novel compounds for use in a method for the diagnostic or therapeutic treatment of the human or animal body, and to processes for the preparation of these compounds.

Background of the invention

A large number of retroviruses have been identified and characterized in recent efforts to understand causes for certain diseases. Among these retroviruses are viruses affecting, e.g., cats, such as FIV, apes, such as SIV, and humans, such as HTLV-I or HIV, especially HIV-1 or HIV-2. A characteristic of these retroviruses is that the transcription of their RNA is controlled by regulatory proteins which bind to hairpin stem-loop RNA conformations present on mRNA's of the retrovirus.

HIV (especially HIV-1) is a virus which is regarded as causative agent for the complex disease process leading to AIDS. The genome of this virus encodes (inter alia) two regulatory proteins, Tat and Rev, which act through regulatory pathways that were identified recently and are controlled at the level of protein-RNA interaction. Two classes of HIV mRNAs can be distinguished. The first of these consists of a doubly spliced, 2 kb mRNA species that encodes the viral regulatory proteins, including Tat and Rev. The second class consists of the unspliced (9 kb) and incompletely spliced (4 kb) viral mRNAs that encode the virion structural proteins. Tat induces a marked increase in the steady-state level of viral mRNA. Evidence suggests that this increase can be explained by an increase in the rate of HIV transcription ("transcription booster"). On the other hand, in the absence of Rev, viral RNA transcripts are fully spliced by the cellular RNA processing machinery prior to export to the cytoplasm. In the presence of Rev unspliced (Gag) or partially spliced (Env) viral mRNAs evade processing - instead they are exported directly to the cytoplasm. Rev indu-

ces the efficient export of viral RNA species that are otherwise excluded from the cell cytoplasm. Both Tat and Rev recognize regulatory elements on the viral mRNA. Tat function is mediated through a sequence termed TAR (for trans-activation response region) that comprises part of the 5'-noncoding region of all HIV mRNAs. This region forms a stable stem-loop structure in vitro. Recent evidence indicates that Tat binds directly to the TAR RNA sequence and that this binding is independent of the nucleotide sequence in the loop but dependent on the integrity of the upper stem. The action of Rev protein is highly sequence specific and requires recognition of an RNA target sequence, the Rev Responsive Element (RRE), a highly conserved region in the middle of the viral env gene. The RRE corresponds to a predicted RNA secondary structure of great stability. The RNA binding sites of both Tat and Rev map to protein areas which are highly arginine rich (see Calnan, B.J., et al., Science 252, 1167-1171 (1991) and Tiley, L.S., et al., Proc. Natl. Acad. Sci. USA 89, 758-62 (1992)).

According to WHO estimations, now more than 20 million people are infected with the retrovirus HIV, this infection usually leading to the death of the infected persons due to the development of AIDS and secondary diseases, such as infections, e.g. by Pneumocystis carinii, and/or tumor diseases.

The Tat/TAR interaction has been investigated in more detail in the literature (see Calnan, B.J., et al., Science 252, 1167-1171 (1991)) and Calnan, B.J., et al., in: Peptides: Chemistry and Biology, Proc. XII Amer. Peptide Symp., ed. by J.A. Smith and J.E. Rivier, ESCOM Science, Leiden 1992, pp. 685-7). Towards the carboxyl terminus of Tat a highly basic region (residues 48 - 57) is present which appears to be involved in RNA binding. It is of high therapeutic interest to identify new chemical entities with the ability to bind HIV RNA at sites of specific regulatory elements (TAR and RRE), and compete in this process with the viral Tat and Rev proteins. Disruptions of Tat/TAR and Rev/RRE complexes corrupt the regulatory systems essential for viral replication and provide a powerful basis for therapeutic intervention in AIDS patients. Different strains of HIV produce different forms of Tat; however, the the N-terminal amino acid sequence of 72 amino acids is common to all forms. The principle form of Tat (designated as Tat(1-86) herein) consists of 86 amino acids in known linear sequence (see Ratner et al., Nature 313, 277 (1985), which is incorporated by reference herein). Three domains in the protein have been shown to exist by structure/function analysis, including a proline-rich region spanning residues 1-18, a cysteine-rich region

spanning residues 22-37, and a basic region of nine amino acid spanning residues 49-57 with the sequence
^{49}(L)-Arg-(L)-Lys-(L)-Lys-(L)-Arg-(L)-Arg-(L)-Gln-(L)-Arg-(L) -Arg-(L)-Arg^{57},
the latter basic region being designated as "basic domain" of the HIV Tat protein.

On the other hand, the binding sites for Tat and Rev on the respective mRNA comprises sites with hairpin stem-loop conformations with so-called bulged residues. For example, Tat is introduced to the transcription machinery following direct binding to an RNA stem-loop structure transcribed from the trans-activation responsive region (TAR). Tat recognizes a U-rich bulge sequence located six residues below the apex of the TAR RNA stem-loop.

Summary of the Invention

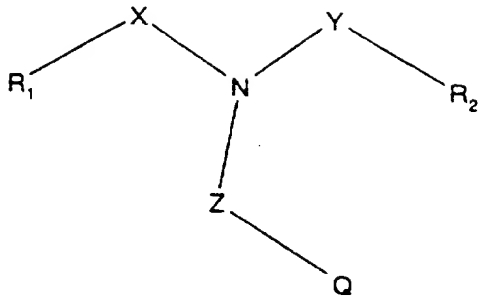
Surprisingly, it has been found that the compounds of formula I defined below show very favourable and valuable pharmaceutical characteristics, especially with regard to the therapeutic and/or diagnostic treatment of retroviral infections, particularly AIDS.

More specifically, the compounds of formula I can be used in the as treatment of a retroviral disease in a warm-blooded animal which disease is responsive to the inhibition of the interaction of a transcriptional regulator with a retroviral response element, that is as antiretroviral compounds and therapeutics inhibiting the interaction of transcriptional regulators with retroviral response elements, for example the interaction between HIV-1 Tat and TAR and/or the interaction between HIV-1 Rev and RRE.

Due to the mechanism that provides these compounds with an incomparable therapeutic potential to complement or replace existing, specific or less specific antiviral treatments, the use of the compounds of the present invention is of particularly high value for the treatment of various retroviral infections, e.g. against variants of HIV, especially such variants that have become resistant to other kinds of treatment.

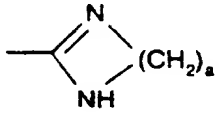
Detailed desciption of the invention

A compound to be used according to the invention is a compound of the formula I,



(I)

wherein

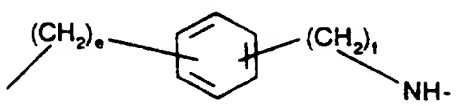
R_1 and R_2 are, independently of each other, a basic group selected from amino, N-alkylamino, N,N-dialkylamino, cycloalkylamino, amidino, N-lower alkylamidino, N,N-di-lower alkylamidino, guanidino, N-lower alkylguanidino, N,N-di-lower alkylguanidino and a group of the formula 

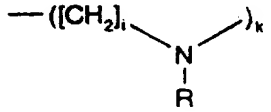
;

X and Y are a bivalent radical independently selected from the group consisting of

$-(CH_2)_b-$, $-CH_2-(CH=CH-)_cCH_2-$, $-CH_2-(C\equiv C-)_dCH_2-$ and

$-(CH_2)_g$-Cycloalkylen-$(CH_2)_h-$,

Z is, independently of X and Y, $-(CH_2)_b-$ or is a bivalent radical of the formula 

or of the formula 

, wherein R is hydrogen or lower alkyl, said bivalent radical being bound via its $-(CH_2)_e-$ or $-(CH_2)_f-$ to the nitrogen and via its -NH- or -N(R)- to Q in formula I,

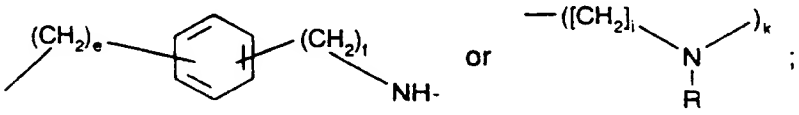
Q is selected from aryl, arylcarbonyl, arylaminocarbonyl, heterocyclyl, heterocyclylcarbonyl or heterocyclylaminocarbonyl, aryl or heterocyclyl whenever mentioned containing 2 or more annelated rings,

a is 2 to 4,

b is 2 to 7,

c, d, e and f is 1 to 3, respectively,
g and h is 0 to 3, respectively,
i is 2 to 7 and
k is 1 to 3,

with the proviso that Q is arylcarbonyl, arylaminocarbonyl, heterocyclylcarbonyl or heterocyclylaminocarbonyl only if Z is a bivalent radical of the formula



;

a tautomer thereof, or a salt thereof.

The compounds of formula I can exist as isomers or mixtures of isomers; for example, if one or more asymmetric carbon atoms are present, these carbon atoms can be in the (R)-, (S)- or (R,S)-configuration, independent of one another. It is thus possible to obtain isomeric mixtures, such as racemates or diastereomeric mixtures, or pure diastereomers or enantiomers, depending on the number of asymmetric carbon atoms and on whether isomers or isomeric mixtures are present. Preferred are pure isomers (enantiomers or diastereomers).

Unless otherwise indicated, the general terms and names used in the description of the present invention preferably have the following meanings:

The term "lower" defines a moiety with up to and including maximally 7, especially up to and including maximally 4, carbon atoms, said moiety being branched or straight-chained. Lower alkyl, for example, is methyl, ethyl, n-propyl, sec-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl or n-heptyl.

In alkylamino, alkyl preferably has up to 12 carbon atoms and is linear or branched one or more times; preferred is lower alkyl, especially C_1-C_4-Alkyl.

Cycloalkyl preferably has 3 to 10, especially 3 to 8 carbon atoms, for example in cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

In N-lower alkylamidino [-C(=NH)-NH-lower alkyl] and N,N-di-lower alkylamidino [-C(=NH)-N(lower alkyl)$_2$], lower alkyl is most preferably methyl or ethyl.

In N-lower alkylguanidino [-NH-C(=NH)-NH-lower alkyl] or N,N-di-lower alkylguanidino [-NH-C(=NH)-N(lower alkyl)$_2$], lower alkyl is most preferably methyl or ethyl.

Cycloalkylene is a bivalent radical which preferably has 3 to 10, more preferably 3 to 8, carbon atoms and is most preferably cyclopropylene (), 1,2- or 1,3-cyclobutylene, 1,2- or 1,3-cyclopentylene or 1,2-, 1,3- or 1,4-cyclohexylene.

Aryl comprising 2 or more annelated rings has preferably from 9 to 16 ring carbon atoms, such as in indenyl, indanyl, naphthyl, anthryl, phenanthryl, acenaphthyl or fluorenyl, and may be unsubstituted or substituted by one or more substitutens, especially unsubstituted or mono- to tri-substituted preferably by lower alkyl, for example methyl, ethyl or propyl, halo-lower alkyl, for example trifluoromethyl, phenyl, 1- or 2-naphthyl, oxo, hydroxy, lower alkoxy, for example methoxy, carbamoyl-lower alkoxy, N-lower alkylcarbamoyl-lower alkoxy or N,N-di-lower alkylcarbamoyl-lower alkoxy, amino, mono- or di-lower alkylamino, lower alkanoylamino, halogen, for example fluorine, chlorine or bromine, carboxy, lower alkoxycarbonyl, phenyl-, naphthyl- or fluorenyl-lower alkoxycarbonyl, such as benzyloxycarbonyl, lower alkanoyl, sulfo, lower alkanesulfonyl, for example methanesulfonyl (CH_3-S(O)$_2$-), phosphono (-P(=O)(OH)$_2$), hydroxy-lower alkoxy phosphoryl or di-lower alkoxyphosphoryl, carbamoyl, mono- or di-lower alkylcarbamoyl, sulfamoyl, mono- or di-lower alkylaminosulfonyl, nitro and/or by cyano.

In arylcarbonyl, aryl is preferably as defined above for aryl.

In arylaminocarbonyl, aryl is preferably as defined above for aryl.

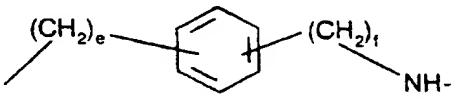
Heterocyclyl comprising 2 or more annelated rings is preferably a double or triple ring system having from 8 to 16 ring atoms, is bonded preferably *via* a carbon atom or (if a nitrogen atom is present) *via* a nitrogen atom (preferably so that only tertiary nitrogen is the binding group in the respective compound of formula I, that is, a hydrogen atom of a corres-

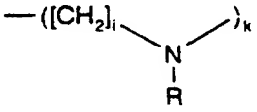
ponding compound Q-H with H bound to the nitrogen is replaced with the moiety Z binding to the rest of the molecule in formula I) and contains up to 4 hetero atoms selected from oxygen, nitrogen, sulfur, and sulfur linked to 1 or 2 oxygen atoms;
which ring system in addition may also be fused to 1 or 2 phenyl rings; and
which ring system may be unsaturated (preferred) or partially or fully saturated,
more preferably a heterocyclic ring selected from indolyl, isoindolyl, 4,5,6,7-tetrahydro indolyl, indolizinyl, *3H*-indolyl, indazolyl, benzo-2-oxy-1,3-diazolyl, purinyl, benzimidazolyl, benzofuranyl, isobenzofuranyl, quinolyl, isoquinolyl, 1,2,3,4-tetrahydroquinolyl or 1,2,3,4--tetrahydroisoquinolyl, *4H*-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, cinnolinyl, pteridinyl, chromenyl, chromanyl, isochromanyl, cyclohexa[b]pyrrolyl, cyclohexa[b]pyridyl, cyclohexa[b]pyrazinyl, cyclohexa [b]pyrimidinyl, xanthenyl, phenoxythiinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, 2,3-dihydro-2-azaphenalenyl, perimidinyl, phenanthrolinyl, phenazolinyl, phenothiazinyl and phenoxazinyl;
heterocyclyl, especially one of the radicals being mentioned as more preferred, being unsubstituted or substituted by one or more, especially one to three, substituents selected from lower alkyl, for example methyl, phenyl, 1- or 2-naphthyl, phenyl-lower alkyl, for example benzyl, hydroxy-lower alkyl, for example hydroxymethyl or 2-hydroxyethyl, hydroxy, lower alkoxy, for example methoxy or ethoxy, amino, lower alkylamino, for example methyl-, ethyl- or tert-butyl-amino, di-lower alkylamino, for example dimethyl- or diethyl-amino, carboxy, lower alkoxycarbonyl, for example methoxy-, isopropoxy-, sec-butoxy- or tert--butoxy-carbonyl, phenyl- or naphthyl-lower alkoxycarbonyl, for example benzyloxycarbonyl, halogen, for example fluorine, chlorine, bromine or iodine, especially chlorine or bromine, lower alkanoyl, for example acetyl or pivaloyl, nitro, oxo and cyano.

It is clear that , if two or more substitutents are present, any substituents in aryl or heterocyclyl are chosen independently of each other.

Most preferably, heterocyclyl comprising 2 or more annelated rings is selected from purinyl, such as purin-6-yl, acridinyl (dibenzo[b,e]pyridyl), such as acridin-4-yl or acridin-9-yl, 1,8-naphthalimidyl (1,3-dioxo-2,3-dihydro-2-azaphenalenyl), such as 1,8-naphthalimido, or benzo-2-oxy-1,3-diazolyl, such as benzo-2-oxy-1,3-diazol-4-yl, each of which is unsubstituted or substituted with one or more, preferably 1 to 3, most preferably 1 or 2 substituents selected preferably from hydroxy, lower alkoxy, such as methoxy, halogen, such as chloro,

and nitro; heterocyclyl is especially selected from 2-chloro-purin-6-yl, acridin-4-yl, acridin-9-yl, 6-chloro-2-methoxy-acridin-9-yl, 1,8-naphthalimido, 3-hydroxy-1,8-naphthalimido, 4-chloro-1,8-naphthalimido and 7-nitro-benzo-2-oxa-1,3-diazol-4-yl.

If heterocyclyl is bound to a nitrogen atom in Z (if Z is 

or ) it is preferably bound via a carbon atom. If heterocylyl is bound to a carbon atom in Z (if Z is $-(CH_2)_b-$) , it is preferably a nitrogen-containing ring system that is bound via a ring nitrogen atom (preferably so that only tertiary nitrogen is the binding group in the respective compound of formula I). These preferred variants of a compound of formula I are preferred at all levels of definitions.

In heterocyclylcarbonyl, heterocyclyl is preferably as defined above for heterocyclyl, especially as one of the preferred heterocyclyl moieties, and is bound preferably via a ring carbon atom. More preferably, heterocyclylcarbonyl is selected from acridinylcarbonyl, such as acridin-4-yl-carbonyl or acridin-9-ylcarbonyl.

In heterocyclylaminocarbonyl, heterocyclyl is preferably as defined above for heterocyclyl and is bound preferably via a ring carbon.

Among the variables,
a is preferably 2 or 3,
b is preferably 2, 3, 4, 5 or 6 in the radicals X and Y or 2, 3 or 4 in the radical Z,
c is preferably 1,
d is preferably 1,
e is preferably 1,
f is preferably 1,
g is preferably 1,
h is preferably 1,
i is preferably 2 to 4, and

k is preferably 1.

Tautomers may, for example, be present if any one of R_1 and R_2 is N-alkylamidino [the possible tautomers being -C(=NH)-NH-lower alkyl ↔ -C(=N-lower alkyl)-NH_2], N-lower alkylguanidino [the possible tautomers being selected from -NH-C(=NH)-NH-lower alkyl ↔ -N=C(NH_2)-NH-lower alkyl ↔ -NH-C(NH_2)=N-lower alkyl], or N,N-di-lower alkylguanidino [the possible tautomers being selected from -NH-C(=NH)-N(lower alkyl)$_2$ ↔ -N=C(NH_2)-N(lower alkyl)$_2$]. The presence and possible conditions for the existence of these tautomers or further tautomers are known to the person having skill in the art. Any of these tautomers are comprised by the definition of compounds of formula I.

Salts are especially pharmaceutically acceptable salts of compounds of formula I.

Such salts are formed, for example, from compounds of formula I having an acid group, for example a carboxy group, a sulfo group, or a phosphoryl group substituted by one or two hydroxy groups, and are, for example, salts thereof with suitable bases, such as non-toxic metal salts derived from metals of groups Ia, Ib, IIa and IIb of the Periodic Table of the Elements, especially suitable alkali metal salts, for example lithium, sodium or potassium salts, or alkaline earth metal salts, for example magnesium or calcium salts, also zinc salts or ammonium salts, as well as salts formed with organic amines, such as unsubstituted or hydroxy-substituted mono-, di- or tri-alkylamines, especially mono-, di- or tri-lower alkyl-amines, or with quaternary ammonium compounds, for example with N-methyl-N-ethyl-amine, diethylamine, triethylamine, mono-, bis- or tris-(2-hydroxy-lower alkyl)amines, such as mono-, bis- or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butyl amine or tris(hydroxy-methyl)methylamine, N,N-di-lower alkyl-N-(hydroxy-lower alkyl)- amines, such as N,N-dimethyl-N-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, N-methyl-D-glucamine, or quaternary ammonium salts, such as tetrabutylammonium salts. The compounds of formula I having a basic group, for example an amino group, can form acid addition salts, for example with inorganic acids, for example hydrohalic acids, such as hydrochloric acid, sulfuric acid or phosphoric acid, or with organic carboxylic, sulfonic, sulfo or phospho acids or N-substituted sulfamic acids, for example acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methyl maleic acid, fumaric acid, malic acid, tar-

taric acid, gluconic acid, glucaric acid, glucuronic acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosali cylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid or isonicotinic acid, as well as with amino acids, for example the a-amino acids mentioned hereinbefore, especially glutamic acid and aspartic acid, and with methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzene sulfonic acid, 4-methylbenzenesulfonic acid, naphthalene-2-sulfonic acid, 2- or 3-phosphoglycerate, glucose-6-phosphate, N-cyclohexylsulfamic acid (forming cycla mates) or with other acidic organic compounds, such as ascorbic acid. Compounds of formula I with acid and basic groups can also form internal salts.

For isolation or purification purposes, it is also possible to use pharmaceutically unaccept able salts, for example perchlorates or picrates.

The compounds of formula I have useful, in particular pharmacologically useful, properties. Surprisingly, it has been found that the compounds of formula I are able to inhibit the propagation of HIV, especially HIV-1, in infected human lymphocytes and show a particularly potent, specific inhibition on the binding of the Tat protein to TAR, mainly by binding to TAR. They thus represent a totally new class of inhibitors and therapeutics.

The in vitro inhibition of the interaction between Tat and TAR can be shown by a competition Tat-TAR gel-shift assay. Through binding of the protein (recombinant Tat, Medical Research Council (MRC), Cambridge, U.K. - the sequence of recombinant Tat can be found in Churcher et al., J. Mol. Biol. 230, 90-110 (1993) to the RNA (synthetic TAR duplex, Genset, Paris, France; the sequence can be found in Hamy et al., J. Mol. Biol. 230, 111-123 (1993)), the overall size and the charge/weight ratio of the formed duplex are changed, so that electrophoretic migration through a native polyacrylamide gel is affected. By radioactive labelling of the RNA and subsequent autoradiography, free RNA and complexes can be discriminated based on their relative positions in the gel (Hamy et al., J. Mol. Biol. 230, 111-123 (1993)). If the binding reaction with a substance able to prevent the protein binding to the radiolabelled RNA, this competition for binding can be visualized on the autoradiography as a decreased intensity of the retarded band. In more detail, compounds of the formula I are tested as follows:

The 14-mer strand of duplex TAR-RNA is labelled in the presence of T4 polynucleotide kinase (New England Biolabs, Beverly, MA, USA) using [γ-^{32}P]ATP (Amersham, Little Chalfont, UK), 10 mM DTT (=dithiothreitol), 50 mM Tris.HCl (pH 7.4, Tris = Tris(hydroxy-methyl)aminomethane), 0.77 % (w/v) spermidine (Fluka, Switzerland) and 10 units T4 polynucleotide kinase incubated at 37 °C for 20 min. After heat-treatment (65 °C, 10 min) for enzyme inactivation, the unincorporated [γ-^{32}P]ATP is removed by chromatography through a sephadex NAP-10 column (Pharmacia, Uppsala, Sweden) equilibrated with water. Prior to the in-vitro-binding reaction, the labelled 14-mer is annealed to 1.5 equivalents of unlabelled 17-mer by heating to 90 C for 3 min, followed by slow cooling down to 0 °C. The binding reaction for protein and RNA which takes place in a volume of 25 ml contains approximately 10,000 cpm of the labelled duplex TAR-RNA and 20 nM recombinant Tat protein in TK buffer (Tris.HCl 20 mM pH 8.0, KCl 50 mM) with 10 mM DTT, 0.1 % Triton X-100 ((Alkylphenylpolyethylenglykol, Rohm & Haas, Darmstadt, Germany) in the absence or presence of varying concentrations of inhibitor. The autoradiographies are quantified by Phosphorimager (Molecular Dynamics/Bucher, Basle, Switzerland). An IC_{50} value is determined as the concentration of a compound of the formula I giving a 50 % decrease in the intensity of the retarded band (Tat-TAR complex). It is possible to show that similar binding affinity can be found when wild-type unlabelled TAR-RNA is used as competitor, thus suggesting that the compounds of the present invention have affinities comparable to that of the high molecular weight full-length Tat protein in vitro.

The IC_{50}-values that are obtained are preferably in the range of from 1×10^{-9} to 1×10^{-6} M. It is necessary to mention that the test data may show variations from assay to assay due to variations in the biological materials; however, relative values determined in one assay and overlap in at least some tested compounds in different assays allow for the comparability of the effectiveness of compounds in different assays.

The in vitro inhibition of the interaction between Rev and RRE can be shown by a competition Rev-RRE gel-shift assay. Through binding of the protein (recombinant Rev, Medical Research Council (MRC), Cambridge, U.K. - the sequence of recombinant Rev can be found in Heaphy et al., Cell 60, 685-93 (1993) to the RNA (synthetic RRE duplex, Genset, Paris, France; the sequence can be found in Iwai et al., Nucl. Acids Res. 20, 6465-72 (1992)), the overall size and the charge/weight ratio of the formed duplex are changed, so

that electrophoretic migration through a native polyacrylamide gel is affected. By radioactive labelling of the RNA and subsequent autoradiography, free RNA and complexes can be discriminated based on their relative positions in the gel (Hamy et al., J. Mol. Biol. 230, 111-123 (1993)). If the binding reaction with a substance able to prevent the protein binding to the radiolabelled RNA, this competition for binding can be visualized on the auto-radiography as a decreased intensity of the retarded band. In more detail, compounds of the formula I are tested as follows:

The 14-mer strand of duplex RRE-RNA is labelled in the presence of T4 polynucleotide kinase (New England Biolabs, Beverly, MA, USA) using [γ-^{32}P]ATP (Amersham, Little Chalfont, UK), 10 mM DTT (=dithiothreitol), 50 mM Tris.HCl (pH 7.4, Tris = Tris(hydroxy-methyl)aminomethane), 0.77 % (w/v) spermidine (Fluka, Switzerland) and 10 units T4 polynucleotide kinase incubated at 37 °C for 20 min. After heat-treatment (65 °C, 10 min) for enzyme inactivation, the unincorporated [γ-^{32}P]ATP is removed by chromatography through a sephadex NAP-10 column (Pharmacia, Uppsala, Sweden) equilibrated with water. Prior to the in-vitro-binding reaction, the labelled 14-mer is annealed to 1.5 equivalents of unlabelled 15-mer by heating to 90 C for 3 min, followed by slow cooling down to 0 °C. The binding reaction for protein and RNA which takes place in a volume of 25 ml contains approximately 10,000 cpm of the labelled duplex RRE-RNA and 20 nM recombinant Rev protein in TK buffer (Tris.HCl 20 mM pH 8.0, KCl 50 mM) with 10 mM DTT, 0.1 % Triton X-100 ((Alkylphenylpolyethylenglykol, Rohm & Haas, Darmstadt, Germany) in the absence or presence of varying concentrations of inhibitor. The autoradiographies are quantified by Phosphorimager (Molecular Dynamics/Bucher, Basle, Switzerland). An IC_{50} value is determined as the concentration of a compound of the formula I giving a 50 % decrease in the intensity of the retarded band (Rev-RRE complex). It is possible to show that similar binding affinity can be found when wild-type unlabelled TAR-RNA is used as competitor, thus suggesting that the compounds of the present invention have affinities comparable to that of the high molecular weight full-length Rev protein in vitro.

The IC_{50}-values that are obtained are preferably in the range of from 1×10^{-9} to 1×10^{-6} M.

In addition, the inhibition of viral growth of HIV-1 in cellular systems in vitro can be demonstrated by procedures known in the art, e.g. according to the method described in Lazdins

et al., AIDS Research and Human Retroviruses 8(4), 505 -11 (1992). In brief, Peripheral Blood Mononuclear Lymphocytes (PBLs) are obtained from the blood of healthy volunteers by leukapheresis. Cells (1 x 10^6/ml) are cultured for 2 days in RPMI-1640 (Gibco), supplemented with 10 % heat-inactivated fetal calf serum (Gibco), 50 mg/ml streptomycin, 50 U/ml penicillin (Amimed), 2 nM glutamine and 10 mM hepes buffer (Gibco). Stimulated lymphocytes are obtained by culturing in the presence of PHA (0.25 mg/ml; Wellcome diagnostics, Templehill, Dartford, England). PHA-lymphocyte stimulation is confirmed by the increase in cell size (Scattergram, FACS analysis). Cells are exposed to HIV-1/LAV.04 (see Barre-Sinoussi et al., Science 220, 868-871 (1983)) for 6 h. Following infection, the cells are washed and resuspended in RPMI-1640 (see above) supplemented with human IL-2 (Genzyme, Cambridge, MA) at 0.6 x 10^6/ml. Medium is changed every 3 days and activity of viral reverse transcriptase (RT activity) is determined in cell supernatants, serving as a measure for the presence of virus and thus of progression of infection according to known procedures (see Willey et al., J. Virol. 62, 353-8 (1991) for details of the method). In brief, RT determination is possible as follows: The RT activity is determined in 50mM of tris-(α,α,α-tris(hydroxymethyl)methylamine, ultra pure, Merck, Federal Republic of Germany) pH 7.8; 75mM of KCl, 2mM of dithiothreitol, 5mM of $MgCl_2$; 0.05% Nonidet P-40 (detergent; Sigma, Switzerland); 50 µg/ml of polyadenylic acid (Pharmacia, Sweden); 1.6 µg/ml of dT(12-18) (Sigma, Switzerland). The mixture is filtered through an Acrodisc filter (0.45µ: Gellman Science Inc, Ann Arbor) and stored at -20°C. 0.1% (v/v) [α-^{32}P]dTTP is added to aliquots of that solution in order to achieve a final radioactive activity of 10µCi/ml. 10µl of the culture supernatant are transferred to a new 96-well microtitre plate and 30µl of the mentioned RT cocktail are added thereto. After mixing, the plate is incubated for from 1.5 to 3hours at 37°C. 5 µl of that reaction mixture are transferred to Whatman DE81 paper (Whatman, Maidstone, UK). The dried filters are washed three times for 5 minutes with 300 mM of NaCl/25mM of trisodium citrate and once with 95% ethanol and again air-dried. Evaluation is effected in a Matrix Packard 96-well counter (Packard, Downers Grove, IL, USA). The RT activity is a measure of the reproduction of HIV-1. The compounds of formula I inhibit virus reproduction when administered in the micromolar range, for example during 18 days after infection practically no increase in RT activity can be determined in the presence of preferably 5 to 50 µM concentrations of an inhibitor of the present invention (for example 0 to 100 counts per minute), while in the control high increase of RT activity can be found (for example more than 2000 counts per minute on day 18).

It can be shown that inhibition by a compound of formula I is mainly due to its ability to permeate into cells, a fact that can be demonstrated by a Fusion Induced Gene Stimulation Assay (FIGS-assay) that excludes cell surface effects as the underlying mechanism of action.

Cellular toxicity experiments are conducted on two cell lines, lymphomic CEM-SS and epitheloid Hela cells (obtainable through the AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH, catalogue No. 776 and 153, respectively). Cells are propagated as monolayer cultures in DMEM-medium, 10% heat inactivated fetal bovine serum (FBS) (both from Gibco, Paisley, UK), supplemented with 100 U/ml penicillin, 100 mg/ml streptomycin, and 2 mM L-glutamine (all from Amimed, Muttenz, CH). Compounds are added to the medium on day 1 and 4, cells are harvested and living cells are counted on day 3 and day 6. With most of the compounds toxicity (> 50 % dead cells) is observed only at a final concentration exceeding 30 μM.

In order to determine its pharmacokinetics, a compound of formula I can be dissolved e.g. in dimethyl sulfoxide (DMSO) in a concentration of 240 mg/ml. The resulting solutions are diluted 1:20 (v/v) with 20 % (w/v) aqueous hydroxypropyl-β-cyclodextrin solution in order to obtain a concentration of the test compound in question of 12 mg/ml. The resulting solution is treated briefly with ultrasound and administered orally to female BALB/c mice (Bomholtgarden, Copenhagen, Denmark) by artificial tube feeding at a dose of 120 mg/kg. At fixed times (for example 30, 60, 90, 120 min) after administration, mice are sacrificed and the plasma stored in heparinised test tubes. The blood is centrifuged (12 000 x g, 5 min) and the plasma removed. The plasma is deproteinised by the addition of an equal volume of acetonitrile. The mixture is mixed using a vortex mixer and and left to stand at room temperature for 20 to 30 minutes. The precipitate is pelleted by centrifugation (12 000 x g, 5 min), and the concentration of the test compound is determined by reversed phase high performance liquid chromatography (HPLC).

The HPLC analysis of the samples obtained in accordance with the method described above is, for example, carried out on a 125 x 4.6 mm Nucleosil® C_{18}-column (reversed-phase material supplied by Macherey & Nagel, Düren, Germany, based on silica gel

derivatised with carbon radicals having 18 carbon atoms), using a 2 cm long preliminary column of the same column material. The test is carried out with the following linear acetonitrile/water gradient (in each case in the presence of 0.05 % trifluoroacetic acid): 20 % acetonitrile to 100 % acetonitrile for 20 min; then 5 min 100% acetonitrile; then returning to the initial conditions for 1 min and 4 min reequilibration. The flow rate is 1 ml/min. The test compound is detected by UV absorption measurement at 255 nm. Peaks are identified by the retention time and the UV spectrum between 205 and 400 nm. The concentrations are determined by the external standard method; the peak heights are obtained for determining the concentrations by comparison with standard curves. The standard curves are obtained by analogous HPLC analysis of mouse plasma that contains known concentrations of the test compound in question and that has been worked up in accordance with the method described above.

The compounds of formula I can thus be used in the treatment of retroviral diseases in warm-blooded animals which diseases are responsive to the inhibition of the interaction of transcriptional regulators with retroviral response elements, preferably HIV-, such as HIV-1-, infections which are responsive to the inhibition of the interaction between Tat and TAR and/or Rev and RRE; and more specifically for the treatment of AIDS and its initial stages, such as ARDS, in humans by inhibition of the interaction between Tat and TAR and/or Rev and RRE of HIV-1. Also treatment of infected cells, e.g. lymphocytes, outside the body is possible in order to reintroduce healthy cells by transplantantion or injection, for example in order to improve the lymphocyte titer in patients with advanced AIDS.

The compounds of formula I can also be used in the treatment of commercially valuable cell (such as lymphocyte) cultures against retroviral infections, especially against HIV, such as HIV-1, infections.

In general, the present invention relates also to the use of a compound of formula I in the inhibition of the interaction of transcriptional regulators with retroviral response elements, especially as mentioned above.

The compounds of the invention may be used either on their own or in combination with other pharmacologically active substances, for example together with inhibitors of reverse

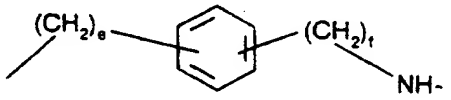
transcriptase, inhibitors of retroviral aspartate protease inhibitors or other antiretrovirally active substances and preparations.

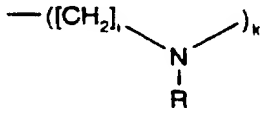
In the case of the preferred subjects of the invention mentioned hereinafter, instead of the general expressions there may be used the more specific definitions mentioned at the begining, where appropriate and expedient.

The invention preferably relates to a use (in the processes, methods and/or pharmaceutical preparations or their preparation as defined above and below) of a compound of formula I wherein

R_1 and R_2 are, independently of each other, a basic group selected from amino, N-alkyl-amino, N,N-dialkylamino, cycloalkylamino, amidino, N-lower alkylamidino, N,N-di-lower alkyl-amidino, guanidino, N-lower alkylguanidino and N,N-di-lower alkylguanidino,

X and Y are independently a bivalent radical of the formula $-(CH_2)_b-$

Z is a bivalent radical of the formula  or

 , wherein R is hydrogen or lower alkyl, said bivalent radical being

bound via its $-(CH_2)_e-$ or $-(CH_2)_f-$ to the nitrogen and via its -NH- or -N(R)- to Q in formula I,

Q is selected from aryl, arylcarbonyl, arylaminocarbonyl, heterocyclyl, heterocyclylcarbonyl or heterocyclylaminocarbonyl, especially from heterocyclyl and heterocyclylcarbonyl; aryl or heterocyclyl whenever mentioned containing 2 or more annelated rings,

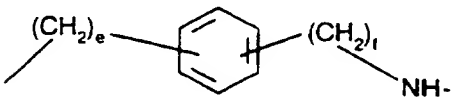
aryl comprising 2 or more annelated rings in the definitions of Q being selected preferably from indenyl, indanyl, naphthyl, anthryl, phenanthryl, acenaphthyl and fluorenyl, which are unsubstituted or substituted by one or more (preferably 1 or 2) substitutents selected from lower alkyl, for example methyl, ethyl or propyl, halo-lower alkyl, for example trifluoromethyl, phenyl, 1- or 2-naphthyl, oxo, hydroxy, lower alkoxy, for example methoxy, carbamoyl-lower

alkoxy, N-lower alkylcarbamoyl-lower alkoxy or N,N-di-lower alkylcarbamoyl-lower alkoxy, amino, mono- or di-lower alkylamino, lower alkanoylamino, halogen, for example fluorine, chlorine or bromine, carboxy, lower alkoxycarbonyl, phenyl-, naphthyl- or fluorenyl-lower alkoxycarbonyl, such as benzyloxycarbonyl, lower alkanoyl, sulfo, lower alkanesulfonyl, for example methanesulfonyl (CH_3-S(O)$_2$-), phosphono (-P(=O)(OH)$_2$), hydroxy-lower alkoxy phosphoryl or di-lower alkoxyphosphoryl, carbamoyl, mono- or di-lower alkylcarbamoyl, sulfamoyl, mono- or di-lower alkyl aminosulfonyl, nitro and cyano;

and heterocyclyl comprising 2 or more annelated rings being selected preferably from indolyl, isoindolyl, 4,5,6,7-tetrahydro indolyl, indolizinyl, *3H*-indolyl, indazolyl, benzo-2-oxy-1,3-diazolyl, purinyl, benzimidazolyl, benzofuranyl, isobenzofuranyl, quinolyl, isoquinolyl, 1,2,3,4-tetrahydroquinolyl or 1,2,3,4-tetrahydroisoquinolyl, *4H*-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, cinnolinyl, pteridinyl, chromenyl, chromanyl, isochromanyl, cyclohexa[b]pyrrolyl, cyclohexa[b]pyridyl, cyclohexa[b]pyrazinyl, cyclohexa[b]pyrimidinyl, xanthenyl, phenoxythiinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, 2,3-dihydro-2-azaphenalenyl, perimidinyl, phenanthrolinyl, phenazolinyl, phenothiazinyl and phenoxazinyl, each of which is unsubstituted or substituted by one or more, especially one to three, more especially 1 or 2, substituents selected from lower alkyl, for example methyl, phenyl, 1- or 2-naphthyl, phenyl-lower alkyl, for example benzyl, hydroxy--lower alkyl, for example hydroxymethyl or 2-hydroxyethyl, hydroxy, lower alkoxy, for example methoxy or ethoxy, amino, lower alkylamino, for example methyl-, ethyl- or tert-butyl-amino, di-lower alkylamino, for example dimethyl- or diethyl-amino, carboxy, lower alkoxycarbonyl, for example methoxy-, isopropoxy-, sec-butoxy- or tert-butoxy-carbonyl, phenyl- or naphthyl-lower alkoxycarbonyl, for example benzyloxycarbonyl, halogen, for example fluorine, chlorine, bromine or iodine, especially chlorine or bromine, lower alkanoyl, for example acetyl or pivaloyl, nitro, oxo and cyano,

b is 2 to 7, preferably 2 to 6,
e and f is 1 to 3, respectively,
i is 2 to 7, preferably 2 to 4, and
k is 1;

with the proviso that Q is arylcarbonyl, arylaminocarbonyl, heterocyclylcarbonyl or heterocyclylaminocarbonyl only if Z is a bivalent radical of the formula



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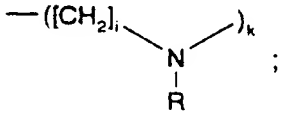
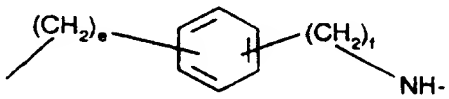


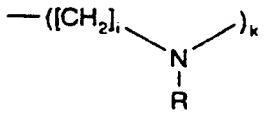
;

a tautomer thereof, or a salt thereof.

Even more preferred is the use of a compound of formula I wherein
R_1 and R_2 each are amino,

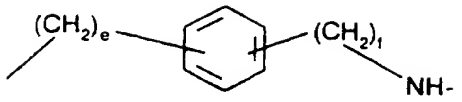
X and Y are independently a bivalent radical of the formula $-(CH_2)_b-$

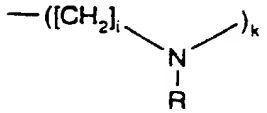
Z is, independently of X and Y, one of the residues mentioned in the definition of X and Y or is a bivalent radical of the formula 

or


, wherein R is hydrogen, said bivalent radical being bound via its $-(CH_2)_e-$ or $-(CH_2)_i-$ to the nitrogen and via its -NH- or -N(R)- to Q in formula I,

Q is selected from purinyl, such as purin-6-yl, acridinyl (dibenzo[b,e]pyridyl), such as acridin-4-yl or acridin-9-yl, 1,8-naphthalimidyl (1,3-dioxo-2,3-dihydro-2-azaphenalenyl), such as 1,8-naphthalimido (bound via its nitrogen atom), and benzo-2-oxy-1,3-diazolyl, such as benzo-2-oxy-1,3-diazol-4-yl, each of which is unsubstituted or substituted with one or more, preferably 1 to 3, most preferably 1 or 2 substituents selected from hydroxy, lower alkoxy, such as methoxy, halogen, such as chloro, and nitro; especially selected from 2-chloro-purin-6-yl, acridin-4-yl, acridin-9-yl, 6-chloro-2-methoxy-acridin-9-yl, 1,8-naphthalimido, 3-hydroxy-1,8-naphthalimido, 4-chloro-1,8-naphthalimido and 7-nitro-benzo-2-oxa-1,3-diazol-4-yl;

or, if Z is a bivalent radical of the formula  or

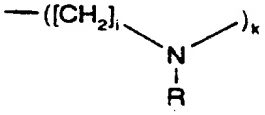
 , Q is acridinylcarbonyl, such as acridin-4-yl-carbonyl or acridin-9-ylcarbonyl;

b is 2 to 7, preferably 2 to 6,
e and f is 1, respectively,
i is 2 to 7, preferably 2 to 4, and
k is 1,

a tautomer thereof, or a salt thereof.

Specifically, the use of compounds of formula I is preferred wherein
R_1 and R_2 each are amino,

X and Y are independently a bivalent radical of the formula $-(CH_2)_b-$,

Z is a bivalent radical of the formula  , wherein R is hydrogen, said bivalent radical being bound via its $-(CH_2)_i-$ to the nitrogen and via its -N(R)- to Q in formula I,

Q is selected from 6-chloro-2-methoxy-acridin-9-yl and acridinylcarbonyl, such as acridin-9-yl-carbonyl or (preferably) acridin-4-ylcarbonyl;

b is 2 to 7, preferably 2 to 6, more preferably 2 to 4,
i is 2 to 4, preferably 3 to 4, and
k is 1,

or a salt thereof.

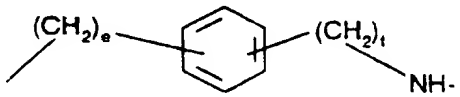
The invention relates also to novel compounds of formula I and their salts and to the use thereof in the processes, methods and pharmaceutical compositions mentioned hereinbefore and hereinafter, and to pharmaceutical compositions comprising those compounds, especially the compounds mentioned below:

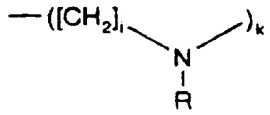
Preferred among these compounds according to the invention is a compound of formula I wherein

R_1 and R_2 are, independently of each other, a basic group selected from amino, N-alkylamino, N,N-dialkylamino, cycloalkylamino, amidino, N-lower alkylamidino, N,N-di-lower alkylamidino, guanidino, N-lower alkylguanidino and N,N-di-lower alkylguanidino;

X and Y are independently a bivalent radical of the formula $-(CH_2)_b-$,

Z is, independently of X and Y, one of the residues mentioned in the definition of X and Y or

is a bivalent radical of the formula  or

 , wherein R is hydrogen or lower alkyl, said bivalent radical being

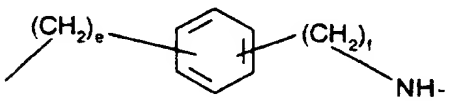
bound via its $-(CH_2)_e-$ or $-(CH_2)_i-$ to the nitrogen and via its -NH- or -N(R)- to Q in formula I,

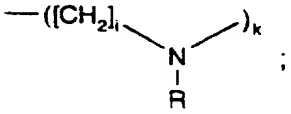
Q is selected from heterocyclyl and heterocyclylcarbonyl, heterocyclyl in both cases being selected from indolyl, isoindolyl, 4,5,6,7-tetrahydro indolyl, indolizinyl, *3H*-indolyl, indazolyl, benzo-2-oxy-1,3-diazolyl, purinyl, benzimidazolyl, benzofuranyl, isobenzofuranyl, isoquinolyl, 1,2,3,4-tetrahydroquinolyl or 1,2,3,4-tetrahydroisoquinolyl, *4H*-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, cinnolinyl, pteridinyl, chromenyl, chromanyl, isochromanyl, cyclohexa[b]pyrrolyl, cyclohexa[b]pyridyl, cyclohexa[b]pyrazinyl, cyclohexa[b]pyrimidinyl, xanthenyl, phenoxythiinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, 2,3-dihydro-2-azaphenalenyl, perimidinyl, phenanthrolinyl, phenazolinyl, phenothiazinyl and phenoxazinyl, each of which is unsubstituted or substituted by one or more, especially one to three, more especially 1 or 2, substituents selected from lower alkyl, for

example methyl, phenyl, 1- or 2-naphthyl, phenyl-lower alkyl, for example benzyl, hydroxy--lower alkyl, for example hydroxymethyl or 2-hydroxyethyl, hydroxy, lower alkoxy, for example methoxy or ethoxy, amino, lower alkylamino, for example methyl-, ethyl- or tert--butyl-amino, di-lower alkylamino, for example dimethyl- or diethyl-amino, carboxy, lower alkoxycarbonyl, for example methoxy-, isopropoxy-, sec-butoxy- or tert-butoxy-carbonyl, phenyl- or naphthyl-lower alkoxycarbonyl, for example benzyloxycarbonyl, halogen, for example fluorine, chlorine, bromine or iodine, especially chlorine or bromine, lower alkanoyl, for example acetyl or pivaloyl, nitro, oxo and cyano,

b is 2 to 7, preferably 2 to 6,
e and f is 1 to 3, respectively,
i is 2 to 7, preferably 2 to 4, and
k is 1,

with the proviso that
(i) Q is heterocyclylcarbonyl only if Z is a bivalent radical of the formula

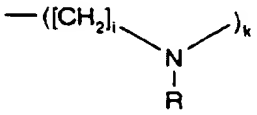


or


;

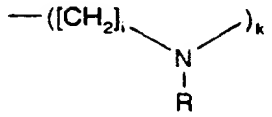
with the further proviso that,

(ii) if each of R_1 and R_2 is amino, Z is a bivalent radical of the formula

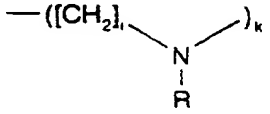


, wherein R is hydrogen or lower alkyl, X and Y are $-(CH_2)_b-$ and Q is acridin-9-ylcarbonyl or 6-chloro-2-methoxy-acridin-9-yl, then at least in one of the residues X and Y b is 3 or larger;

with the further proviso that

(iii) a compound wherein each of R_1 and R_2 is amino, each of X and Y is $-(CH_2)_6-$, Z is a bivalent radical of the formula  bound as described above wherein i is 3, k is 1 and R is hydrogen, and Q is 6-chloro-2-methoxy-acridin-9-yl is excluded;

and with the further proviso that

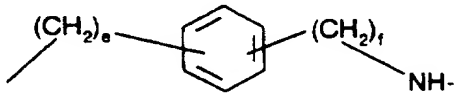
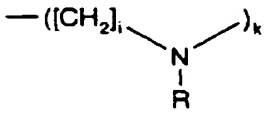
(iv) a compound wherein each of R_1 and R_2 is diethylamino, each of X and Y is $-(CH_2)_3-$, Z is a bivalent radical of the formula  bound as described above wherein i is 2, k is 1 and R is hydrogen, and Q is acridin-9-ylcarbonyl is excluded;

a tautomer thereof, or a salt thereof.

More preferred is a compound of formula I, wherein

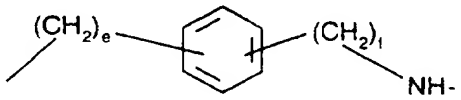
R_1 and R_2 are, independently of each other, a basic group selected from amino, N-alkylamino, N,N-dialkylamino, cycloalkylamino, amidino, N-lower alkylamidino, N,N-di-lower alkylamidino, guanidino, N-lower alkylguanidino and N,N-di-lower alkylguanidino

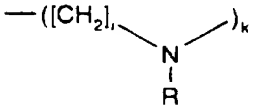
X and Y independently are a group of the formula $-(CH_2)_b-$,

Z is, independently of X and Y, one of the residues mentioned in the definition of X and Y or is a bivalent radical of the formula  or  , wherein R is hydrogen, said bivalent radical being bound via its $-(CH_2)_e-$ or $-(CH_2)_i-$ to the nitrogen and via its -NH- or -N(R)- to Q in formula I,

Q is selected from purinyl, such as purin-6-yl, acridinyl (dibenzo[b,e]pyridyl), such as acridin-4-yl or acridin-9-yl, 1,8-naphthalimidyl (1,3-dioxo-2,3-dihydro-2-azaphenalenyl), such as 1,8-

naphthalimido, and benzo-2-oxy-1,3-diazolyl, such as benzo-2-oxy-1,3-diazol-4-yl; preferably from purinyl, such as purin-6-yl, acridinyl (dibenzo[b,e]pyridyl), such as acridin-4-yl or acridin-9-yl, 1,8-naphthalimidyl (1,3-dioxo-2,3-dihydro-2-azaphenalenyl), except for 1,8-naphthalimido; or benzo-2-oxy-1,3-diazolyl, such as benzo-2-oxy-1,3-diazol-4-yl, being

bound to a moiety Z of formula  or

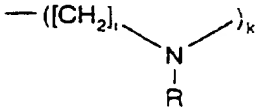
 and 1,8-naphthalimido being bound to -$(CH_2)_b$- as Z;

each of which is unsubstituted or substituted with one or more, preferably 1 to 3, most preferably 1 or 2 substituents selected from hydroxy, lower alkoxy, such as methoxy, halogen, such as chloro, and nitro; especially selected from 2-chloro-purin-6-yl, acridin-4-yl, acridin-9-yl, 6-chloro-2-methoxy-acridin-9-yl, 1,8-naphthalimido, 3-hydroxy-1,8-naphthalimido, 4-chloro-1,8-naphthalimido and 7-nitro-benzo-2-oxa-1,3-diazol-4-yl;

or is acridinylcarbonyl, such as acridin-4-yl-carbonyl or acridin-9-ylcarbonyl,

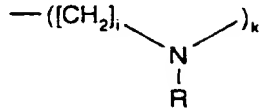
b is 2 to 6,
e and f is 1, respectively,
i is 2 to 4 and
k is 1,

with the proviso that

(i) Q is acridinylcarbonyl only if Z is a bivalent radical of the formula  ;

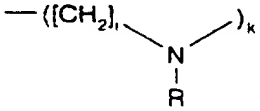
with the further proviso that,

(ii) if each of R_1 and R_2 is amino, Z is a bivalent radical of the formula

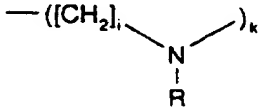


, wherein R is hydrogen, X and Y are $-(CH_2)_b-$ and Q is acridin-9-ylcarbonyl or 6-chloro-2-methoxy-acridin-9-yl, then at least in one of the residues X and Y b is 3 or larger;

with the further proviso that

(iii) a compound wherein each of R_1 and R_2 is amino, each of X and Y is $-(CH_2)_6-$, Z is a bivalent radical of the formula  bound as described above wherein i is 3, k is 1 and R is hydrogen, and Q is 6-chloro-2-methoxy-acridin-9-yl is excluded;

and with the further proviso that

(iv) a compound wherein each of R_1 and R_2 is diethylamino, each of X and Y is $-(CH_2)_3-$, Z is a bivalent radical of the formula  bound as described above wherein i is 2, k is 1 and R is hydrogen, and Q is acridin-9-ylcarbonyl is excluded;

a tautomer thereof, or a salt thereof.

Even more preferred is a compound of formula I wherein
each of R_1 and R_2 is amino,
X and Y independently are a group $-(CH_2)_b-$,
Z is, independently of X and Y, $-(CH_2)_b-$,

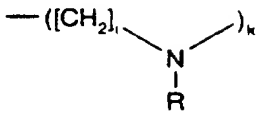
Q is selected from 1,8-naphthalimido which is unsubstituted or substituted with one or more, preferably 1 to 3, most preferably 1 or 2 substituents selected from hydroxy, lower alkoxy, such as methoxy, halogen, such as chloro, and nitro; most preferably selected from 1,8-naphthalimido, 3-hydroxy-1,8-naphthalimido and 4-chloro-1,8-naphthalimido;

b is 2 to 6, and
e and f is 1, respectively,

or a salt thereof.

Also even more preferred is a compound of formula I, wherein
each of R_1 and R_2 is amino,

X and Y are independently a group $-(CH_2)_b-$,

Z is a bivalent radical of the formula  , wherein R is hydrogen, said bivalent radical being bound via its $-(CH_2)_i-$ to the nitrogen and via its -N(R)- to Q in formula I,

Q is selected from purinyl, such as purin-6-yl, and benzo-2-oxy-1,3-diazolyl, such as benzo-2-oxy-1,3-diazol-4-yl, each of which is unsubstituted or substituted with one or more, preferably 1 to 3, most preferably 1 or 2 substituents selected from hydroxy, lower alkoxy, such as methoxy, halogen, such as chloro, and nitro,

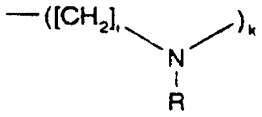
or is acridinyl (dibenzo[b,e]pyridyl), such as acridin-4-yl or acridin-9-yl;

especially selected from 2-chloro-purin-6-yl, acridin-4-yl, acridin-9-yl, 3-hydroxy-1,8-naphthalimidyl, 4-chloro-1,8-naphthalimidyl and 7-nitro-benzo-2-oxa-1,3-diazol-4-yl;

or is acridin-4-yl-carbonyl,

b is 2 to 6,
e and f is 1, respectively,
i is 2 to 4 and
k is 1,

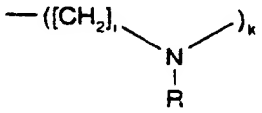
with the proviso that

a compound wherein each of R_1 and R_2 is diethylamino, each of X and Y is $-(CH_2)_3-$, Z is a bivalent radical of the formula  bound as described above wherein i is 2, k is 1 and R is hydrogen, and Q is acridin-9-ylcarbonyl is excluded;

or a salt thereof.

Also even more preferred is a compound of formula I, wherein
each of R_1 and R_2 is amino,

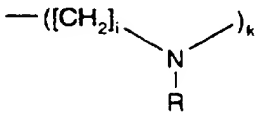
X and Y are independently a group $-(CH_2)_b-$,

Z is a bivalent radical of the formula  , wherein R is hydrogen, said bivalent radical being bound via its $-(CH_2)_i-$ to the nitrogen and via its -N(R)- to Q in formula I,

Q is acridinyl (dibenzo[b,e]pyridyl), such as acridin-4-yl or acridin-9-yl; which is unsubstituted or substituted with one or more, preferably 1 to 3, most preferably 1 or 2 substituents selected from hydroxy, lower alkoxy, such as methoxy, halogen, such as chloro, and nitro, or is acridinylcarbonyl, such as acridin-9-yl-carbonyl,

b is 3 to 6,
e and f is 1, respectively,
i is 2 to 4 and
k is 1,

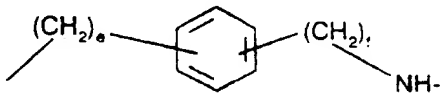
with the proviso that

a compound wherein each of R_1 and R_2 is diethylamino, each of X and Y is $-(CH_2)_3-$, Z is a bivalent radical of the formula  bound as described above wherein i is 2, k is 1 and R is hydrogen, and Q is acridin-9-ylcarbonyl is excluded;

or a salt thereof.

Very preferred is also a compound of formula I, wherein
R_1 and R_2 are, independently of each other, a basic group selected from amino (especially prefered), N-alkylamino, N,N-dialkylamino, cycloalkylamino, amidino, N-lower alkylamidino, N,N-di-lower alkylamidino, guanidino, N-lower alkylguanidino and N,N-di-lower alkylguanidino,

X and Y are a bivalent radical independently selected from the group consisting of $-(CH_2)_b-$ (very preferred), $-CH_2-(CH=CH-)_cCH_2-$, $-CH_2-(C\equiv C-)_dCH_2-$ and $-(CH_2)_g$-Cycloalkylen-$(CH_2)_h-$,

Z is a bivalent radical of the formula  , said bivalent radical being bound via its $-(CH_2)_e-$ to the nitrogen and via its -NH- to Q in formula I,

Q is selected from heterocyclyl and heterocyclylcarbonyl, heterocyclyl being bound via a ring carbon atom and being selected from indolyl, isoindolyl, 4,5,6,7-tetrahydro indolyl, indolizinyl, *3H*-indolyl, indazolyl, benzo-2-oxy-1,3-diazolyl, purinyl, benzimidazolyl, benzofuranyl, isobenzofuranyl, quinolyl, isoquinolyl, 1,2,3,4-tetrahydroquinolyl or 1,2,3,4-tetrahydroisoquinolyl, *4H*-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, cinnolinyl, pteridinyl, chromenyl, chromanyl, isochromanyl, cyclohexa[b]pyrrolyl, cyclohexa[b]pyridyl, cyclohexa[b]pyrazinyl, cyclohexa[b]pyrimidinyl, xanthenyl, phenoxythiinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, 2,3-dihydro-2-azaphenalenyl, perimidinyl, phenanthrolinyl, phenazolinyl, phenothiazinyl and phenoxazinyl, each of which is unsubsti-

tuted or substituted by one or more, especially one to three, more especially 1 or 2, substituents selected from lower alkyl, for example methyl, phenyl, 1- or 2-naphthyl, phenyl-lower alkyl, for example benzyl, hydroxy-lower alkyl, for example hydroxymethyl or 2-hydroxyethyl, hydroxy, lower alkoxy, for example methoxy or ethoxy, amino, lower alkylamino, for example methyl-, ethyl- or tert-butyl-amino, di-lower alkylamino, for example dimethyl- or diethyl-amino, carboxy, lower alkoxycarbonyl, for example methoxy-, isopropoxy-, sec-butoxy- or tert-butoxy-carbonyl, phenyl- or naphthyl-lower alkoxycarbonyl, for example benzyloxycarbonyl, halogen, for example fluorine, chlorine, bromine or iodine, especially chlorine or bromine, lower alkanoyl, for example acetyl or pivaloyl, nitro, oxo and cyano,

b is 2 to 7, preferably 2 to 6,
c, d, e and f are 1 to 3, respectively, and
g and h are 0 to 3, respectively,

a tautomer thereof, or a salt thereof.

Most preferred is the use of a compound of formula I or a novel compound of formula I mentioned in the examples, or a (preferably pharmaceutically acceptable) salt thereof.

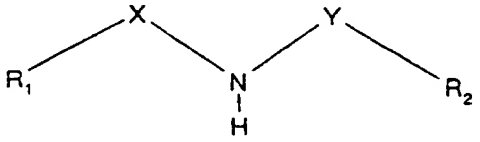
Especially preferred is a compound of the formula I named
5-(3-{6-chloro-2-methoxy-acridin-9-yl}-aminopropyl)-1,5,10-triazadecane,
5-(2-{4-acridinoyl}-aminoethyl)-1,5,10-triazadecane,
N-(3-[1,5,10-triazadecan-5-yl]-propyl)-3-nitro-1,8-naphthalimide,
N-(2-[1,5,10-triazadecan-5-yl]-ethyl)-1,8-naphthalimide,
N-(3-[1,5,10-triazadecan-5-yl]-propyl)-4-chloro-1,8-naphthalimide,
N-(2-[1,5,10-triazadecan-5-yl]-ethyl)-3-hydroxy-1,8-naphthalimide,
5-(3-{6-chloro-2-methoxy-acridin-9-yl}-aminopropyl)-1,5,9-triazanonane,
6-(3-{6-chloro-2-methoxy-acridin-9-yl}-aminopropyl)-1,6,11-triazaundecane,
5-(4-{6-chloro-2-methoxy-acridin-9-yl}-aminobutyl)-1,5,10-triazadecane or
5-(2-{6-chloro-2-methoxy-acridin-9-yl}-aminoethyl)-1,5,10-triazadecane,
or a pharmaceutically acceptable salt thereof, respectively.

Especially preferred is also a compound of the formula I named

5-(5-{6-chloro-2-methoxy-acridin-9-yl}-aminopentyl)-1,5,10-triazadecane or 6-(4-{6-chloro-2-methoxy-acridin-9-yl}-aminopentyl)-1,6,11-triazaundecane, or a pharmaceutically acceptable salt thereof, respectively.

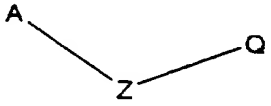
The compounds of the formula I can be synthesized according to procedures that are known *per se*, but not with regard to the new compounds of formula I mentioned above and below, especially by a process comprising

a) reacting an imino compound of the formula II



(II)

wherein R_1, R_2, X and Y are defined as for compounds of formula I, with a compound of formula III,



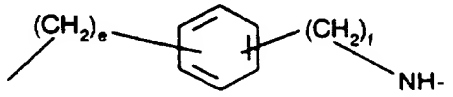
(III)

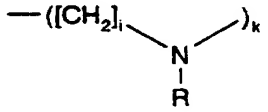
wherein

Z and Q are as defined for compounds of formula I and

A is a nucleofugal leaving group, the starting materials where necessary being present in protected form, and removing any protecting groups being present; or

b) for the synthesis of a compound of formula I

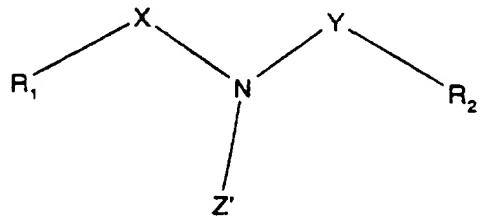
wherein Z is a bivalent moiety of the formula 

or of the formula 

, wherein R, e, f, i and k are as defined for compounds of formula I,

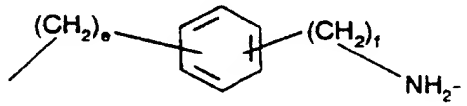
Q is aryl, arylcarbonyl, heterocyclyl that is not bound via a ring nitrogen atom or heterocyclylcarbonyl

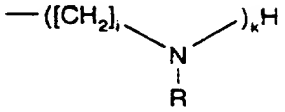
and e, f, i, k, R_1, R_2, X and Y are as defined for compounds of formula I,
reacting an amino compound of the formula IV,



(IV)

wherein R_1, R_2, X and Y are as defined for compounds of formula I and

Z' is 

or 

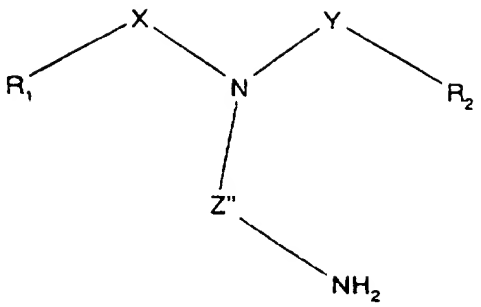
wherein R, e, f, i and k are as defined for compounds of formula I,
with a compound of formula V,

Q-L (V)

wherein
Q is aryl, arylcarbonyl, heterocyclyl that is not bound via a ring nitrogen atom or heterocyclylcarbonyl and
L is a leaving group,
the starting materials where necessary being present in protected form, and removing any protecting groups being present; or

c) for the synthesis of a compound of formula I wherein
Z is $-(CH_2)_b-$, wherein b is as defined for a compound of formula I,
Q is unsubstituted or substituted 1,8-naphthalimido and
R_1, R_2, X, Y and b are as defined for a compound of formula I,

reacting an amino compound of the formula VI,



(VI)

wherein

Z" is $-(CH_2)_b-$, and

R_1, R_2, X and Y are as defined for a compound of formula I,

with unsubstituted or substituted 1,8-naphthalene-dicarboxylic acid or a reactive derivative thereof,

the starting materials where necessary being present in protected form, and removing any protecting groups being present;

and, if desired, transforming a compound of formula I into a different compound of formula I, transforming a salt of an obtainable compound of formula I into the free compound or a different salt or an obtainable free compound of formula I into a salt, and/or separating obtainable mixtures of isomers of compounds of formula I into the individual isomers.

In the following, more detailed description of the preferred process conditions, R_1, R_2, X, Y, Z, Q, a, b, c, d, e, f, g, h, i and k have the meanings given for compounds of the formula I, if not mentioned otherwise. All starting materials can also be used in the form of salts where salt-forming groups are present and where the presence of the salts does not lead to undesired side reactions.

Process a) (alkylation):

In starting materials of the formulae II and III, functional groups, with the exception of the groups which are to take part in the reaction or do not react under the reaction conditions, are, independently of each other, protected by protective groups.

Protective groups for functional groups in starting materials whose reaction is to be avoided, in particular carboxyl, amino and hydroxyl groups, include, in particular, those protective groups (conventional protecting groups) which are customarily used in the synthesis of peptide compounds or else of cephalosporins and penicillins, and also nucleic acid derivatives and sugars. These protective groups can already be present in the precursors and are intended to protect the functional groups concerned against unwanted side reactions such as acylations, etherifications, esterifications, oxidations, solvolysis, etc. In certain cases, the protective groups can, in addition to this, have the effect of making the course of reactions selective, for example stereoselective. It is characteristic of protective groups that they are easily detachable, i.e. without undesirable side reactions, for example solvolytically, reductively, photolytically or else enzymically, for example under physiological conditions as well, and that they are not present in the end products.

The protection of functional groups by such protective groups (introduction of protecting groups), the protective groups themselves, and also the reactions for eliminating them, are described, for example, in standard works such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in Th. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides"; Volume 3 (E. Gross and J. Meienhofer, editors), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (Methods of Organic Chemistry), HoubenWeyl, 4th Edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" (Amino Acids, Peptides and Proteins), Verlag Chemie, Weinheim, Deerfield Beach and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of the Carbohydrates: Monosaccharides and Derivatives), Georg Thieme Verlag, Stuttgart 1974.

The skilled person will know how to select protecting groups or combinations of protecting groups and methods for the introduction and removal of protecting groups or combinations of protecting groups that are useful in the desired reaction steps.

A carboxyl group is, for example, protected as an ester group which can be selectively cleaved under mild conditions. A carboxyl group which is protected in esterified form is primarily esterified with a lower alkyl group which is preferably branched in the 1 position of the lower

alkyl group or is substituted by suitable substituents in the 1 or 2 position of the lower alkyl group.

A protected carboxyl group which is esterified with a lower alkyl group is, for example, methoxycarbonyl or ethoxycarbonyl.

A protected carboxyl group which is esterified with a lower alkyl group which is branched in the 1 position of the lower alkyl group is, for example, tert-lower-alkoxycarbonyl, for example tert-butoxycarbonyl.

A protected carboxyl group which is esterified with a lower alkyl group which is substituted in the 1 or 2 position of the lower alkyl group by suitable substituents is, for example, 1-aryl-lower-alkoxycarbonyl, such as arylmethoxycarbonyl, having one or two aryl radicals, in which aryl is phenyl which is unsubstituted or is substituted once, twice or three times by, for example, lower alkyl, for example tert-lower-alkyl, such as tert-butyl, lower alkoxy, for example methoxy, hydroxyl, halogen, for example chlorine, and/or nitro, for example benzyloxycarbonyl, benzyloxycarbonyl which is substituted by the said substituents, for example 4-nitrobenzyloxycarbonyl or 4-methoxybenzyloxycarbonyl, diphenylmethoxycarbonyl or diphenylmethoxycarbonyl which is substituted by the said substituents, for example di-(4-methoxyphenyl)methoxycarbonyl, and, in addition, carboxyl which is esterified with a lower alkyl group, where the lower alkyl group is substituted in the 1 or 2 position by suitable substituents, such as 1-lower-alkoxy-lower-alkoxycarbonyl, for example methoxymethoxycarbonyl, 1-methoxyethoxycarbonyl or 1-ethoxyethoxycarbonyl, 1-lower-alkylthio-lower-alkoxycarbonyl, for example 1-methylthiomethoxycarbonyl or 1-ethylthioethoxycarbonyl, aroylmethoxycarbonyl, in which the aroyl group is benzoyl which is unsubstituted or substituted, for example, by halogen, such as bromine, for example phenacyloxycarbonyl, 2-halo-lower-alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodethoxycarbonyl, and also 2-(trisubstituted silyl)-lower-alkoxycarbonyl, in which the substituents, independently of each other, are in each case an aliphatic, araliphatic, cycloaliphatic or aromatic hydrocarbon radical which is unsubstituted or substituted, for example, by lower alkyl, lower alkoxy, aryl, halogen and/or nitro, for example lower alkyl which is unsubstituted or substituted as above, phenyl-lower alkyl, cycloalkyl or phenyl, for example 2-tri-lower-alkylsilyl-lower-alkoxycarbonyl, such as 2-tri-lower-alkylsilylethoxycarbonyl, for

example 2-trimethylsilylethoxycarbonyl or 2-(di-n-butylmethylsilyl)ethoxycarbonyl, or 2-triarylsilylethoxycarbonyl, such as triphenylsilylethoxycarbonyl.

A carboxyl group can also be protected as an organic silyloxycarbonyl group. An organic silyloxycarbonyl group is, for example, a tri-lower-alkylsilyloxycarbonyl group, for example trimethylsilyloxycarbonyl. The silicon atom of the silyloxycarbonyl group can also be substituted by two lower alkyl, for example methyl, groups, and an amino or carboxyl group of a second molecule of the formula I. Compounds possessing such protective groups can be prepared, for example, using corresponding tri-lower-alkylhalosilanes, such as tert-butyldimethylchlorosilane, as silylating agents.

A carboxyl group is also protected in the form of an internal ester with a hydroxyl group which is present in the molecule at a suitable distance, for example in the g position with regard to the carboxyl group, i.e. in the form of a lactone, preferably a g-lactone.

A protected carboxyl group is preferably tert-lower-alkoxycarbonyl, for example tert-butoxycarbonyl, benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 9-fluorenylmethoxycarbonyl or diphenylmethoxycarbonyl, or a protected carboxyl group in the form of a lactone, in particular a g-lactone.

A protected amino group is protected by an amino protecting group, for example in the form of an acylamino, arylmethylamino, etherified mercaptoamino, 2-acyl-lower-alk-1-enylamino or silylamino group, or as an azido group.

In an acylamino group, acyl is, for example, the acyl radical of an organic carboxylic acid having, for example, up to 18 carbon atoms, in particular of a lower-alkanecarboxylic acid which is unsubstituted or substituted, for example, by halogen or aryl, or of benzoic acid which is unsubstituted or substituted, for example, by halogen, lower alkoxy or nitro, or, preferably, of a carbonic acid semiester. Such acyl groups are, preferably, lower alkanoyl, such as formyl, acetyl, propionyl or pivaloyl, halo-lower-alkanoyl, for example 2-haloacetyl, such as 2-chloro-, 2-bromo-, 2-iodo-, 2,2,2-trifluoro- or 2,2,2-trichloroacetyl, benzoyl which is unsubstituted or substituted, for example, by halogen, lower alkoxy or nitro, such as benzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl or 4-nitrobenzoyl, lower-alkoxycarbonyl, lower-alkoxycarbonyl which is preferably branched in the 1 position of the lower-alkyl radical or is

suitably substituted in the 1 or 2 position, for example tert-lower-alkoxycarbonyl, such as tert-butoxycarbonyl, 1-aryl-lower-alkoxycarbonyl, such as arylmethoxycarbonyl, having one, two or three aryl radicals which are phenyl which is unsubstituted or substituted once or more than once by, for example, lower alkyl, in particular tert-lower-alkyl, such as tert-butyl, lower alkoxy, such as methoxy, hydroxyl, halogen, such as chlorine, and/or nitro, for example benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, diphenylmethoxycarbonyl, 9-fluorenylmethoxycarbonyl or di-(4-methoxyphenyl)methoxycarbonyl, aroylmethoxycarbonyl, in which the aroyl group is benzoyl which is unsubstituted or preferably substituted, for example, by halogen, such as bromine, for example phenacyloxycarbonyl, 2-halo-lower-alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodoethoxycarbonyl, 2-(tri-substituted silyl)-lower-alkoxycarbonyl, for example 2-tri-lower-alkylsilyl-lower-alkoxycarbonyl such as 2-trimethylsilylethoxycarbonyl or 2-(di-n-butyl-methylsilyl)ethoxycarbonyl, or triarylsilyl-lower-alkoxycarbonyl, for example 2-triphenylsilyl-ethoxycarbonyl.

In an arylmethylamino group, for example a mono-, di- or, in particular, tri-arylmethylamino group, the aryl radicals are, in particular, phenyl radicals which are unsubstituted or substituted. Examples of such groups are benzyl-, diphenylmethyl- or, in particular, trityl-amino.

In an etherified mercaptoamino group, the mercapto group is primarily present as substituted arylthio or aryl-lower-alkylthio in which aryl is, for example, phenyl which is unsubstituted or substituted, for example, by lower alkyl, such as methyl or tert-butyl, lower alkoxy, such as methoxy, halogen, such as chlorine, and/or nitro, for example 4-nitrophenylthio.

In a 2-acyl-lower-alk-1-enyl radical which can be used as an amino protective group, acyl is, for example, the corresponding radical of a lower-alkanecarboxylic acid, of a benzoic acid which is unsubstituted or substituted, for example, by lower alkyl, such as methyl or tert-butyl, lower alkoxy, such as methoxy, halogen, such as chlorine, and/or nitro, or, in particular, of a carbonic acid semiester, such as a carbonic acid lower-alkyl semiester. Corresponding protective groups are, primarily, 1-lower-alkanoyl-lower-alk-1-en-2-yl, for example 1-lower-alkanoyl-prop-1-en-2-yl, such as 1-acetyl-prop-1-en-2-yl, or lower-alkoxycarbonyl-lower-alk-1-en-2-yl, for example lower-alkoxycarbonyl-prop-1-en-2-yl, such as 1-ethoxycarbonyl-prop-1-en-2-yl.

A silylamino group is, for example, a tri-lower-alkylsilylamino group, for example trimethylsilylamino or tert-butyldimethylsilylamino. The silicon atom of the silylamino group can also only be substituted by two lower alkyl groups, for example methyl groups, and the amino group or carboxyl group of a second molecule of the formula I. Compounds having such protective groups can be prepared, for example, using the corresponding chlorosilanes, such as tert-butyldimethylchlorosilane, as silating agents.

An amino group can also be protected by conversion into the protonated form; suitable corresponding anions are primarily those of strong inorganic acids, such as of sulfuric acid, phosphoric acid or hydrohalic acids, for example the chlorine or bromine anion, or of organic sulfonic acids, such as p-toluenesulfonic acid.

Preferred amino protective groups are lower-alkoxycarbonyl, phenyl-lower-alkoxycarbonyl, fluorenyl-lower-alkoxycarbonyl, 2-lower-alkanoyl-lower-alk-1-en-2-yl or lower-alkoxycarbonyl-lower-alk-1-en-2-yl, especially tert-butoxycarbonyl or benzyloxycarbonyl.

A hydroxyl group can, for example, be protected by an acyl group, for example lower alkanoyl which is unsubstituted or substituted by halogen, such as chlorine, such as acetyl or 2,2-dichloroacetyl, or, in particular, by an acyl radical, which is specified for protected amino groups, of a carbonic acid semiester. A hydroxyl group can also be protected by tri-lower-alkylsilyl, for example trimethylsilyl, triisopropylsilyl or tert-butyldimethylsilyl, a readily detachable etherifying group, for example an alkyl group, such as tert-lower-alkyl, for example tert-butyl, an oxa- or a thia-aliphatic or -cycloaliphatic, in particular 2-oxa- or 2-thia-aliphatic or -cycloaliphatic, hydrocarbon radical, for example 1-lower-alkoxy-lower-alkyl or 1-lower-alkylthio-lower-alkyl, such as methoxymethyl, 1-methoxymethyl, 1-ethoxymethyl, methylthiomethyl, 1-methylthioethyl or 1-ethylthioethyl, or 2-oxa- or 2-thia-cycloalkyl having 5-7 ring atoms, such as 2-tetrahydrofuryl or 2-tetrahydropyranyl, or a corresponding thia analogue, and also by 1-phenyl-lower-alkyl, such as benzyl, diphenylmethyl or trityl, with it being possible for the phenyl radicals to be substituted, for example, by halogen, for example chlorine, lower alkoxy, for example methoxy, and/or nitro. A preferred hydroxyl protective group is, for example, 2,2,2-trichloroethoxycarbonyl, 4-nitrobenzyloxycarbonyl, diphenylmethoxycarbonyl, benzyl or trityl.

Two hydroxyl groups, in particular adjacent hydroxyl groups, which are present in a molecule, or an adjacent hydroxyl group and amino group, can, for example, be protected by bivalent protective groups, such as a methylene group which is preferably substituted, for example by one or two lower alkyl radicals or oxo, for example by unsubstituted or substituted alkylidene, for example lower alkylidene, such as isopropylidene, cycloalkylidene, such as cyclohexylidene, a carbonyl group or benzylidene.

A hydroxyl group which is located adjacent to a carboxyl group can be protected by the formation of an internal ester (lactone), in particular of a g-lactone.

Preferably, a protected hydroxyl group is protected by tri-lower-alkylsilyl or as a lactone, in particular by tert-butyldimethylsilyl or as a g-lactone.

Within the meaning of this application, a polymeric support, as is suitable, for example, for the Merrifield synthesis, and which is bound in an easily detachable manner to the functional group to be protected, for example a carboxyl group, is also expressly understood to be a protective group, for example a carboxyl protective group. A suitable polymeric support of this nature is, in particular, a polystyrene resin which is weakly cross-connected by copolymerization with divinylbenzene and which carries suitable bridge members for the reversible binding.

For the reaction between compounds of formula II and formula III, the nucleofugal leaving group A is preferably a nucleofugal group, preferably arylsulfonyloxy, such as toluenesulfonyloxy, lower alkanesulfonyloxy, such as methanesulfonyloxy, or especially halogen, such as chlorine, bromine or iodine, most especially chlorine.

The reaction is preferably carried out without bases or in the presence of relatively weak bases, such as especially metal hydroxides or carbonates, such as especially alkali metal hydroxides, for example sodium or potassium hydroxide, or in the presence of alkaline earth metal carbonates or alkali metal carbonates, for example sodium or potassium carbonate, preferably in the last-mentioned solvents, especially in halogenated hydrocarbons, such as dichloromethane or chloroform, or in carboxylic acid amides, such as dimethylformamide or dimethylacetamide, or in hydroxyaromates, such as phenol, and preferably at the tempe-

ratures indicated below; or further in the presence of a strong base, such as an alkali metal hydride, for example sodium hydride or potassium hydride, or also an alkali metal amide, such as sodium amide, or an alkali metal di-lower alkylamide, such as lithium diisopropylamide, especially in the presence of sodium hydride or potassium hydride, which may be added, for example, in the form of a dispersion in oil or after extraction of the oil, for example with a liquid hydrocarbon, such as hexane, using the base in an equimolar amount or preferably in excess relative to the molar amount of the compound of formula II, for example in an amount of from 1 to 20 times the molar amount, especially from 1 to 3 times the molar amount, prefeerably in aprotic, especially polar, solvents, such as acid amides, for example dimethylformamide, diethylformamide, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)--pyrimidinone (DMPU) or hexamethylphosphoric acid triamide, aromatic hydrocarbons, such as toluene or benzene (in which case preferably in the presence of a phase transfer catalyst, for example a tetra-lower alkylammonium halide, such as tetra(n-butyl)ammonium bromide), or mixtures of such solvents;
the reaction taking place at preferred temperatures of from -10°C to the reflux temperature of the reaction mixture, especially from approximately 5 to approximately 40°C, for example at room temperature, or at from 50°C to the reflux temperature, for example at from 80 to 110°C, in the presence or absence of a protecting gas, such as argon or nitrogen; ammonia that is formed when alkali metal amides are used as bases is preferably removed by the application of a vacuum, for example of from 0.1 to 100, especially from 0.5 to 10, torr.

Detachment of the protective groups which are not components of the desired end product of the formula I, for example the carboxyl, amino and/or hydroxy protective groups, is effected in a manner known per se, for example using solvolysis, in particular hydrolysis, alcoholysis or acidolysis, or by means of reduction, in particular hydrogenolysis, or by means of other reducing agents, and also photolysis, as desired stepwise or simultaneously, with it also being possible to use enzymatic methods. Detachment of the protective groups is described, for example, in the standard works which are mentioned above in the section on protective groups.

Thus, a protected carboxyl, for example, for example lower-alkoxycarbonyl (which is preferably branched in the 1 position), such as tert-lower-alkoxycarbonyl, lower-alkoxycarbonyl which is substituted in the 2 position by a tri-substituted silyl group or in the 1 position by lower alkoxy or lower-alkylthio, or diphenylmethoxycarbonyl which is unsubstituted or sub-

stituted, can be converted into free carboxyl by treatment with a suitable acid, such as formic acid, acetic acid, oxalix acid, hydrochloric acid or trifluoroacetic acid, if desired while adding a nucleophilic compound, such as phenol or anisole. Benzyloxycarbonyl which is unsubstituted or substituted can, for example, be set free by means of hydrogenolysis, i.e. by treatment with hydrogen in the presence of a metallic hydrogenation catalyst, such as a palladium catalyst. In addition, suitably substituted benzyloxycarbonyl, such as 4-nitrobenzyloxycarbonyl, can also be converted into free carboxyl by reduction, for example by treatment with an alkali metal dithionite, such as sodium dithionite, or with a reducing metal, for example zinc, or a reducing metal salt, such as a chromium(II) salt, for example chromium(II)chloride customarily in the presence of a hydrogen-releasing agent which, together with metal, can produce nascent hydrogen, such as an acid, primarily a suitable carboxylic acid, such as a lower-alkanecarboxylic acid which is unsubstituted or substituted, for example, by hydroxyl, for example acetic acid, formic acid, glycolic acid, diphenylglycolic acid, lactic acid, mandelic acid, 4-chloromandelic acid or tartaric acid, or an alcohol or thiol, with water preferably being added. By means of treating with a reducing metal or metal salt, as described above, 2-halo-lower-alkoxycarbonyl (if desired after converting a 2-bromo-lower-alkoxycarbonyl group into a corresponding 2-iodo-lower-alkoxycarbonyl group) or aroylmethoxycarbonyl can also be converted into free carboxyl. Aroylmethoxycarbonyl can be cleaved by treating with a nucleophilic, preferably salt-forming reagent, such as sodium thiophenoxide or sodium iodide. The carboxyl group can also be set free from 1-aryl-lower-alkoxycarbonyl, for example arylmethoxycarbonyl, such as benzyloxycarbonyl, by hydrolysing in the presence of a base such as an alkali metal hydroxide, for example sodium or potassium hydroxide. 2-(Tri-substituted silyl)-lower-alkoxycarbonyl, such as 2-tri-lower-alkylsilyl-lower-alkoxycarbonyl, can also be converted into free carboxyl by treating with a salt of hydrofluoric acid which provides the fluoride anion, such as an alkali metal fluoride, for example sodium or potassium fluoride, in the absence or presence of a macrocyclic polyether ("crown ether"), or with a fluoride of an organic quaternary base, such as tetra-lower-alkylammonium fluoride or tri-lower-alkylaryl-lower-alkylammonium fluoride, for example tetraethylammonium fluoride or tetrabutylammonium fluoride, in the presence of an aprotic, polar solvent, such as dimethyl sulfoxide, N,N-dimethylformamide or N,N-dimethylacetamide. Carboxyl which is protected as organic silyloxycarbonyl, such as tri-lower-alkylsilyloxycarbonyl, for example trimethylsilyloxycarbonyl, can be released solvolytically in a customary manner, for example by treating with water, an alcohol or acid, or, in addition, fluoride, as described above. Esterified carboxyl can also be set free enzymically, for example using

esterases or suitable peptidases, for example esterified arginine or lysine, such as lysine methyl ester, using trypsin. Carboxyl which is protected as an internal ester, such as a g-lactone, can be released by hydrolysis in the presence of a hydroxide-containing base, such as an alkaline earth metal hydroxide or, in particular, an alkali metal hydroxide, for example NaOH, KOH or LiOH, in particular LiOH, with the corresponding protected hydroxyl group being set free simultaneously.

A protected amino group is set free in a manner which is known per se and which differs depending on the nature of the protective groups, preferably using solvolysis or reduction. Lower-alkoxycarbonylamino, such as tert-butoxycarbonylamino, can be cleaved in the presence of acids, for example mineral acids, for example hydrohalic acid, such as hydrochloric acid or hydrobromic acid, in particular hydrobromic acid, or of sulfuric acid or phosphoric acid, preferably of hydrochloric acid, or of relatively strong organic acids, such as formic acid, oxalic acid, trichloroacetic acid or trifluoroacetic acid, in polar solvents, for example water or a carboxylic acid, such as acetic acid or formic acid, esters, such as lower alkyl lower alkanoates, e.g. ethyl acetate, halohydrocarbons, such as chlorinated lower-alkanes, for example dichloromethane or chloroform, or ethers, preferably cyclic ethers, such as dioxane, or in organic carboxylic acids which are liquid at the reaction temperature, without solvent, for example in formic acid. 2-Halo-lower-alkoxycarbonylamino (if desired, after converting a 2-bromo-lower-alkoxycarbonylamino group into a 2-iodo-lower-alkoxycarbonylamino group), aroylmethoxycarbonylamino or 4-nitrobenzyloxycarbonylamino can, for example, be cleaved by treating with a suitable reducing agent, such as zinc in the presence of a suitable carboxylic acid, such as aqueous acetic acid. Aroylmethoxycarbonylamino can also be cleaved by treating with a nucleophilic, preferably salt-forming, reagent such as sodium thiophenoxide, and 4-nitrobenzyloxycarbonylamino also by treating with an alkali metal dithionite, for example sodium dithionite. Substituted or unsubstituted diphenylmethoxycarbonylamino, tert-lower-alkoxycarbonylamino or 2-(trisubstituted silyl)-lower-alkoxycarbonylamino, such as 2-tri-lower-alkylsilyl-lower-alkoxycarbonylamino, can be cleaved by treating with a suitable acid, for example formic or trifluoroacetic acid, for example in a halogenated hydrocarbon, such as methylene chloride or chloroform (in particular, if hydroxyl which is simultaneously protected with benzyl is not to be set free), 1-aryl-lower-alkoxycarbonylamino, such as substituted or unsubstituted benzyloxycarbonylamino, can, for example, be cleaved by means of hydrogenolysis, i.e. by treating with hydrogen in the presence of a suitable hydrogenation catalyst, such as a palladium catalyst,

for example bound to a support material, such as carbon, preferably in polar solvents, such as di-lower-alkyl-lower-alkanoylamides, for example dimethylformamide, ethers, such as cyclic ethers, for example dioxane, esters, such as lower-alkyl lower-alkanoates, for example ethyl acetate, or alcohols, such as methanol, ethanol or propanol, with methanol being particularly preferred, preferably, for example, at room temperature, substituted or unsubstituted triarylmethylamino or formylamino can be cleaved, for example, by treating with an acid, such as a mineral acid, for example hydrochloric acid, or an organic acid, for example formic, acetic or trifluoroacetic acid, if desired in the presence of water, and triphenylaminomethyl can be cleaved, in particular, by hydrogenolysis using a precious metal or precious metal oxide as catalyst, such as platinum, palladium or, in particular, palladium hydroxide, with the catalyst preferably being bonded to a support material, such as carbon, silica gel or aluminium oxide, in inert solvents, such as an ester, or preferably a lower-alkyl lower-alkanoate, such as ethyl acetate, at temperatures of from 20 to 80°C, in particular of from 50 to 70°C, if required under elevated pressure, for example between about 1 and 10 bar, and an amino group which is protected as silylamino can be set free, for example, by means of hydrolysis or alcoholysis. An amino group which is protected by 2-haloacetyl, for example 2-chloroacetyl, can be set free by treating with thiourea in the presence of a base, or with a thiolate salt, such as an alkali metal thiolate of the thiourea, and subsequent solvolysis, such as alcoholysis or hydrolysis, of the resulting substitution product. An amino group which is protected by 2-(trisubstituted silyl)-lower-alkoxycarbonyl, such as 2-tri-lower-alkylsilyl-lower-alkoxycarbonyl, can also be converted into the free amino group by treating with a fluoride anion-providing salt of the hydrofluoric acid, as indicated above in connection with the release of a correspondingly protected carboxyl group. Silyl, such as trimethylsilyl or tert-butyldimethylsilyl, which is bonded directly to a heteroatom, such as nitrogen, can likewise be detached with fluoride ions, preferably using a fluoride of an organic, quaternary nitrogen base, such as tetra-lower-alkylammonium fluoride or tri-lower-alkylaryl-lower-alkyl-ammonium fluoride, for example tetraethylammonium fluoride or tetrabutylammonium fluoride, in the presence of an aprotic, polar solvent, such as dimethyl sulfoxide or N,N-dimethylacetamide, or, in particular, of an ether, such as tetrahydrofuran, at temperatures between 0 and 50°C, in particular, for example, at room temperature.

Amino which is protected in the form of an azido group is converted into free amino, for example, by means of reduction for example by means of catalytic hydrogenation with hydrogen in the presence of a hydrogenation catalyst, such as platinum oxide, palladium or

Raney nickel, by means of reduction with mercapto compounds, such as dithiothreitol or mercaptoethanol, or by treating with zinc in the presence of an acid, such as acetic acid. The catalytic hydrogenation is preferably carried out in an inert solvent, such as a halogenated hydrocarbon, for example methylene chloride, or else in water or a mixture of water and an organic solvent, such as an alcohol or dioxane, at from approximately 20°C to 25°C, or else while cooling or heating.

A hydroxyl group which is protected by a suitable acyl group, a tri-lower-alkylsilyl group or by substituted or unsubstituted 1-aryl(such as 1-phenyl)-lower-alkyl is set free in an analogous manner to a correspondingly protected amino group. A hydroxyl group or mercapto group which is protected by 2,2-dichloroacetyl is set free, for example, by basic hydrolysis, while a hydroxyl group which is protected by tert-lower-alkyl or by a 2-oxa- or 2-thia-aliphatic or -cycloaliphatic hydrocarbon radical is set free by acidolysis, for example by treating with a mineral acid or a strong carboxylic acid, for example trifluoroacetic acid. A hydroxyl group which is protected by benzyloxy is set free, for example, by means of hydrogenolysis, i.e. by treating with hydrogen in the presence of a suitable hydrogenation catalyst, such as a palladium catalyst, for example bound to a support material, such as charcoal, preferably in polar solvents, such as di-lower-alkyl-lower-alkanoylamides, for example dimethylformamide, ethers, such as cyclic ethers, for example dioxane, esters, such as lower-alkylalkanoates, for example ethyl acetate, chlorinated hydrocarbons, such as dichloromethane, or alcohols, such as methanol, ethanol or propanol, with methanol being particularly preferred, or mixtures of two or more of these solvents, preferably, for example, at room temperature. Two hydroxyl groups, or an adjacent amino group and hydroxyl group, which are together protected by means of a bivalent protective group, preferably, for example, a methylene group which is substituted once or twice by lower alkyl, such as by lower alkylidene, for example isopropylidene, cycloalkylidene, for example cyclohexylidene, or benzylidene, can be set free by acidic solvolysis, particularly in the presence of a mineral acid or a strong organic acid. A tri-lower-alkylsilyl group is likewise detached by means of acidolysis, for example by mineral acid, preferably hydrofluoric acid, or a strong carboxylic acid. Hydroxyl can also preferably be set free from tri-lower-alkylsilyloxy by treating with a fluoride anion-providing salt of hydrofluoric acid, such as an alkali metal fluoride, for example sodium or potassium fluoride, in the absence or presence of a macrocyclic polyether ("crown ether"), or with a fluoride of an organic quaternary base, such as tetra-lower-alkylammonium fluoride or tri-lower-alkylaryl-lower-alkylammonium fluoride, for example tetraethylammonium fluoride or

tetrabutylammonium fluoride, in the presence of an aprotic, polar solvent, such as dimethyl sulfoxide or N,N-dimethylacetamide. 2-Halo-lower-alkoxycarbonyl is removed by the above-mentioned reducing agents, for example reducing metal, such as zinc, reducing metal salts, such as chromium(II) salts, or by sulfur compounds, for example sodium dithionite or, preferably, sodium sulfide and carbon disulfide. Esterified hydroxyl groups, for example lower-alkanoyloxy, such as acetyloxy, can also be set free with esterases, while acylated amino can, for example, be set free using suitable peptidases.

The temperatures for the release of the protected functional groups are preferably between -80°C and the boiling temperature of the reaction mixture, in particular between -80 and 110°C; particularly preferably between -20 and 50°C, for example between 10 and 35°C, such as, for example, at room temperature, or at from 50°C up to the boiling temperature of the reaction mixture concerned, for example at approximately 65°C.

Process b) (alkylation or acylation):

In compounds of formula IV and formula V, functional groups, with the exception of the groups which are to take part in the reaction or do not react under the reaction conditions, are, independently of each other, protected by protective groups. The protective groups and their introduction are analogous to those described in process a).

The leaving group L is preferably arylsulfonyloxy, such as toluenesulfonyloxy, lower alkanesulfonyloxy, such as methanesulfonyloxy, or especially halogen, such as chlorine, bromine or iodine, most especially chlorine, or, especially in the case where Q is arylcarbonyl or heterocyclylcarbonyl, is formed *in situ*, for example from a hydroxy group.

The reaction is preferably carried out without bases or in the presence of relatively weak bases, such as especially metal hydroxides or carbonates, such as especially alkali metal hydroxides, for example sodium or potassium hydroxide, or in the presence of alkaline earth metal carbonates or alkali metal carbonates, for example sodium or potassium carbonate, preferably in the last-mentioned solvents, especially in halogenated hydrocarbons, such as dichloromethane or chloroform, or in carboxylic acid amides, such as dimethylformamide or dimethylacetamide, or in hydroxyaromates, such as phenol, and preferably at the temperatures indicated below; or further in the presence of a strong base, such as an alkali metal

hydride, for example sodium hydride or potassium hydride, or also an alkali metal amide, such as sodium amide, or an alkali metal di-lower alkylamide, such as lithium diisopropylamide, especially in the presence of sodium hydride or potassium hydride, which may be added, for example, in the form of a dispersion in oil or after extraction of the oil, for example with a liquid hydrocarbon, such as hexane, using the base in an equimolar amount or preferably in excess relative to the molar amount of the compound of formula II, for example in an amount of from 1 to 20 times the molar amount, especially from 1 to 3 times the molar amount, prefeerably in aprotic, especially polar, solvents, such as acid amides, for example dimethylformamide, diethylformamide, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)--pyrimidinone (DMPU) or hexamethylphosphoric acid triamide, aromatic hydrocarbons, such as toluene or benzene (in which case preferably in the presence of a phase transfer catalyst, for example a tetra-lower alkylammonium halide, such as tetra(n-butyl)ammonium bromide), or mixtures of such solvents;
the reaction taking place at preferred temperatures of from -10°C to the reflux temperature of the reaction mixture, especially from approximately 5 to approximately 40°C, for example at room temperature, or at from 50°C to the reflux temperature, for example at from 80 to 110°C, in the presence or absence of a protecting gas, such as argon or nitrogen; ammonia that is formed when alkali metal amides are used as bases is preferably removed by the application of a vacuum, for example of from 0.1 to 100, especially from 0.5 to 10, torr.

If Q is arylcarbonyl of heterocyclylcarbonyl, formation of a leaving group L is taking place preferably *in situ*, for example by condensation for preparing the resulting amide bond in the presence of one of the customary condensing agents. Examples of customary condensing agents are carbodiimides, for example diethyl-, dipropyl-, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide or, in particular, dicyclohexylcarbodiimide, and, in addition, suitable carbonyl compounds, for example carbonylimidazole, 1,2-oxazolium compounds, for example 2-ethyl-5-phenyl-1,2-oxazolium-3'-sulfonate and 2-tert-butyl-5-methylisoxazolium perchlorate, or a suitable acylamino compound, for example 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, N,N,N',N'-tetraalkyluronium compounds, such as O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate, and, in addition, activated phosphoric acid derivatives, for example diphenylphosphoryl azide, diethylphosphoryl cyanide (= diethyl cyanophosphonate), phenyl-N-phenylphosphoroamidochloridate, bis(2-oxo-3-oxazolidinyl)phosphinic chloride or 1-benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate.

If necessary or desired, an organic base is added, preferably a tri-substituted nitrogen base, for example a tri-lower-alkylamine, for example with bulky radicals, for example ethyl diisopropylamine, or with unbranched radicals, such as, in particular, triethylamine, and/or a heterocyclic base, for example pyridine, 4-dimethylaminopyridine or, preferably N-methylmorpholine. The base can also be bonded to a polymeric support, for example polystyrene, for example as a "polyhünig base" (= diisopropylaminomethylpolystyrene).

Racemization-lowering reagents, such as N-hydroxybenzotriazole, can also be added, possibly also in combination with organic bases, as defined immediately above.

For the detachment of the protective groups which are not components of the desired end product of formula I the reaction conditions are analogous to those mentioned in the detailed description of process a).

Process c) (condensation):

In compounds of formula VI and unsubstituted or substituted 1,8-anphthalic acid, functional groups, with the exception of the groups which are to take part in the reaction or do not react under the reaction conditions, are, independently of each other, protected by protective groups. The protective groups and their introduction are analogous to those described in process a).

Reactive derivatives of unsubstituted or substituted naphthalene-1,8-dicarbonic acids are preferably reactive esters or especially reactive anhydrides. Reactive carbonic acid derivatives can also be formed in situ.

Reactive esters are, for example, the hydroxybenzotriazole (HOBT), pentafluorophenyl, 4-nitrophenyl or N-hydroxysuccinimide ester of an unsubstituted or substituted naphthalene-1,8-dicarbonic acid.

Preferred as anhydride and as reactive derivative is an unsubstituted or substituted naphthalene-1,8-dicarbonic acid anhydride (internal anhydride).

The reaction steps required for the synthesis of the resulting imide bond usually depend on the type of activation of the carboxylic groups participating in the reaction. The reactions normally run in the presence of a condensing agent or, when activating the carboxylic acids in the form of anhydrides, of an agent that binds the carboxylic acid formed. In some cases it is also possible to add chaotropic agents such as LiF in NB-methylpyrrolidone. The reactions are especially carried out in a temperature range from -30 to +150 °C, preferably from +10 to +70 °C, and, most preferably, from +20 to +50 °C, if appropriate, in an inert gas atmosphere, e.g. under nitrogen or argon.

Especially preferred is the reaction with the respective unsubstituted or substituted naphthalene-1,8-dicarbonic acid anhydride (internal anhydride); the reaction preferably takes place in an appropriate solvent, such as an alkohol, for example methanol, ethanol or especially n-propanol or isopropanol, at the temperatures mentioned above.

Condensation may also proceed with the free unsubstituted or substituted naphthalene-1,8-dicarbonic acid by *in situ* formation of a reactive derivative,
(i) directly with a carbodiimide, e.g. dicyclohexylcarbodiimide (DCC), N-ethyl-N'-(3-di methylaminopropyl)-carbodiimide, N,N'-diethylcarbodiimide or N,N'-diisopropylcarbo diimide (DICD); with a carbonyl compound such as carbonyldiimidazole; with 1,2-ox azolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium-3'-sulfonate and 2-tert- butyl-5-methylisoxazolium perchlorate; with acylamino compounds such as 2-ethoxy- 1-ethoxycarbonyl-1,2-dihydroquinoline; with an uronium compound such as 2-(1H-benzo triazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) or 2-(pyridon- 1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate = O-(1,2-dihydro-2-oxo-1-pyridyl) -N,N,N',N'-tetramethyluronium-tetrafluoroborate (TPTU); or phosphonium compounds such as benzotriazol-1-yl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) or benzotriazol-1-yl-oxy-pyrrolidino-phosphonium hexafluorophosphate (PyBOP);

(ii) via formation of the internal anhydride (obtainable, for example, by condensation of the corresponding acid in the presence of a carbodiimide or 1-diethylaminopropyne; internal anhydrides method), and/or

(iii) by formation of an "active ester", e.g. a hydroxybenzotriazole (HOBT), pentafluorophenyl, 4-nitrophenyl or N-hydroxysuccinimide ester.

Useful acid binding agents that can be employed in the condensation reactions are, for example, alkaline metals, carbonates or bicarbonates, such as sodium or potassium carbonate or bicarbonate (if appropriate, together with a sulfate), or organic bases such as sterically hindered organic nitrogen bases, for example tri-lower alkylamines, such as N,N-diisopropyl-N-ethylamine.

For the detachment of the protective groups which are not components of the desired end product of formula I the reaction conditions are analogous to those mentioned in the detailed description of process a).

Additional process steps

The conversion of a salt of a compound of formula I into a different salt is carried out, for example, in solvents, especially in organic solvents, more especially in polar organic solvents, very especially in esters, for example lower alkanoyl-lower alkyl esters, such as ethyl acetate, in amides, for example N,N-di-lower alkyl-lower alkanoylamides, such as dimethylformamide, in alcohols, for example hydroxy-lower alkanes, such as methanol, ethanol, ethylene glycol or glycerol, or aryl alcohols, such as phenols, for example phenol, or in dimethyl sulfoxide, in the absence or presence of water, preferably in the presence of water, or in water itself. Special preference is given to reaction in alcohols, such as the last-mentioned hydroxy-lower alkanes, in mixtures of such alcohols and water, or in water itself.

The reaction is carried out, for example, in free solution, but it may also be effected over chromatographic columns, for example by gel filtration.

The reaction is carried out at temperatures from immediately above the freezing point to the boiling point of the solutions in question, preferably at from 0 to 50°C, especially at from 20 to 40°C, for example at room temperature, in the presence or absence of a protecting gas, such as nitrogen or argon.

The compounds of formula I and the salt-forming base or acid are used in suitable molar ratios, or the salt forming base or acid is employed in excess. Preferably, the individual components are used in the molar ratio that corresponds to the ratio of the molarity of the base of formulaI and the acid in the resulting salts.

The salts that are formed precipitate, for example, by themselves, in some cases only after cooling, or they are precipitated by the addition of solvents, especially of non-polar solvents, for example ethers, such as diethyl ether, or of water, and/or are obtained by partial or complete concentration by evaporation.

The reaction may also be effected via the free compounds of formula I, which are prepared, for example, by converting the base or acid salt of a base of formula I, with a first base or acid, used as starting material into the free compound with the aid of an acid or base, for example a hydroxy base, such as an alkali metal hydroxide, for example NaOH or KOH, or with an OH^--charged ion exchanger in aqueous solution in the presence or absence of an organic solvent, as defined above; the subsequent conversion of the free compound may be carried out, for example, as described above.

The free compounds of formula I are preferably prepared as just described, also by chromatography, for example by gel filtration, or over ion exchangers.

Mixtures of isomers obtainable according to the invention can be separated in a manner known per se into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Starting materials:

The present invention relates also to novel starting materials and/or intermediates and to processes for their preparation. The starting materials used and the reaction conditions selected are preferably those that result in the compounds described as being preferred.

For the synthesis of new starting materials, conditions and reactants analogous to those described in the Examples are especially preferred.

In the following description of some paradigmatic methods of preparation for starting materials, functional groups that are not to participate in the reaction and which would disturb the desired reaction or lead to side reactions are present in protected form, where required. The protection of functional groups and the respective groups are, for example, analogous to those described under process a) as described above. The removal of protecting groups is possible under customary conditions, preferably as described under process a), and at appropriate reaction stages and steps. The groups that have to be protected are known to the person having skill in the art, and therefore the introduction, presence and/or removal of protecting groups are mentioned only if very important for the process steps described below. Although not especially mentioned, it is clear that the starting materials can also be used in the form of salts where salt-forming groups are present and the formation of salts does not lead to undesired reactions.

An imino compound of the formula II is, for example, either known (see, e.g., WO 89/98998) or accessible, e.g., by reacting a compound of formula VII,

R_1-X-B (VII)

wherein R_1 and X are defined as for formula I and B is a leaving group, especially aryl-sulfonyloxy, such as toluenesulfonyloxy, lower alkanesulfonyloxy, such as methanesulfonyl-oxy, or more especially halogen, such as chlorine, bromine or iodine, with an alkali metal phthalimide salt, such as the potassium salt of phthalimide, cleavage of the resulting phthalimide compound, e.g. by hydrazinolysis, resulting in a compound of the formula IX,

R_1-X-NH_2 (VIII)

wherein R_1 and X are as defined for formula I, if necessary, formation of the respective sulfonamide, e.g. by reaction with p-toluolsulfonylchloride, and reaction with a compound of the formula IX,

R_2-Y-B (IX)

wherein R_2 and Y are as defined for formula I and B is a leaving group, independently as defined for B in formula VII.

Symmetrical compounds of formula II can be obtained conveniently by simultaneous reaction of identical compounds of the formulae VII and IX, wherein R_1=R_2, X=Y, each as defined for formula I, with ammonia (NH_3).

Compounds of formulae VII and IX are known or commercially available, or they can, for example, be prepared conveniently as follows (only preparation of a compound of formula VII is described in detail; however, analogous preparation of a compound of formula IX is possile, if instead of R_1 and X the moieties R_2 and Y are present):

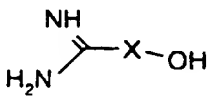
(A) An amidino, N-lower alkyl- or N,N-di-lower alkylamidino compound of formula VII can be prepared, for example, by reaction of a compound of the formula X,

HO-X-B' (X)

wherein X is as defined for formula I and B' is a leaving group as defined for B for formula VII, with an alkalimetal cyanide, e.g. sodium cyanide, thus forming a compound of formula XI,

HO-X-CN (XI)

wherein X is as defined for formula I, and
(i) for the synthesis of an amidino compound by reaction with hydroxylamine, e.g. as (for example, chloride) salt in the presence of an alkali metal alcoholate, such as sodium methylate, and subsequent reduction to the respective amidine of the formula XII



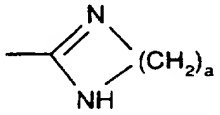
(XII)

wherein X is as defined for formula I, followed by introduction of the leaving group B, e.g. by reaction with an arylsulfonylhalogenide or a lower alkanesulfonylhalogenide and, if desired,

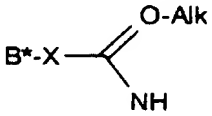
replacement of the resulting arylsulfonyloxy group or lower alkanesulfonyloxy group with a halogenide; or

(ii) for the synthesis of an N-lower alkylamidino group or an N,N-di-lower alkylamidino group by reaction of a compound of the formula XI with an alcohol, such as ethanol, in the presence of a thionylhalogenide, such as thionylchloride, to the corresponding imidoester (= iminoether) halogenide, e.g. the chloride, and subsequent reaction with lower alkylamine or N,N-di-lower alkylamine, followed by introduction of the leaving group B, e.g. by reaction of the hydroxy group with an arylsulfonylhalogenide or a lower alkanesulfonylhalogenide and, if desired, replacement of the resulting arylsulfonyloxy group or lower alkanesulfonyloxy group with a halogenide.

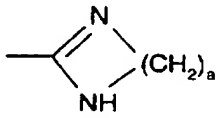
(B) A compound of formula VII wherein guanidino, N-lower alkylguanidino or N,N-di-lower alkylguanidino is present as R_1, can be prepared, for example, by reaction of a compound of formula X, as defined above, with guanidine, N-Alkylguanidine or N,N-di-lower alkylguanidine (or a salt thereof) and subsequent introduction of the leaving group B, e.g. by reaction of the hydroxy group with an arylsulfonylhalogenide or a lower alkanesulfonylhalogenide and, if desired, replacement of the resulting arylsulfonyloxy group or lower alkanesulfonyloxy group with a halogenide.

(C) A compound of formula VII wherein R_1 has the formula 

can be prepared, for example, by reacting am imidoester compound of the formula VII*,

 (VII*)

which is present as an acid addition salt, for example with HCl, and wherein X has the meanings given in formula I, Alk is an alkyl, for example a lower alkyl, group and B* is a protected hydroxy group, with a compound of the formula $H_2N\text{-}(CH_2)_a\text{-}NH_2$, for example by heating in an inert solvent, such as xylene, preferably under reflux, subsequently removing the hydroxy protecting group and replacing the resulting hydroxy by a leaving group B, as

defined for compounds of formula VII, under customary conditions. A compound of the formula VII* can be obtained from the respective nitrile compound B*-X-CN by reaction with an alcohol HO-Alk in the presence of a strong acid, for example HCl. Also by reaction of appropriate acid halogenides of the formula B-X-CO-Hal with a compound of the formula $H_2N-(CH_2)_a-NH_2$ the compounds of formula VII with R_1 =  .can be prepared.

A compound of formula III is known or commercially available, or it can be synthesized according to one of the following procedures:

(A) Reaction of a compound of the formula XIII,

HO-Z' (XIII)

wherein Z' is as defined for a compound of formula IV, with a compound of formula V, as defined under process b), under process conditions analogous to those in process b) leads to a compound of the formula XIV,

HO-Z*-Q (XIV)

wherein Z* is equal to Z', except that the final amino hydrogen is missing and replaced by the bond to Q, and Q is defined as for a compond of formula IV and V, respectively; introduction of a nucleofugal leaving group A, e.g. by reaction of the hydroxy group with an arylsulfonylhalogenide or a lower alkanesulfonylhalogenide and, if desired, replacement of the resulting arylsulfonyloxy group or lower alkanesulfonyloxy group with a halogenide, leads then to a compound of formula III wherein Z is Z'.

(B) Nucleophilic substitution of a compound of the formula XV,

Q*-H (XV)

wherein Q* is nitrogen-containing heterocyclyl containing 2 or more annelated rings that is bound to the hydrogen via a ring nitrogen atom with a compound of the formula

HO-Z''-G (XVI)

wherein Z'' is a moiety of the formula $-(CH_2)_b-$ and G is a nucleofugal leaving group, especially arylsulfonyloxy, such as toluenesulfonyloxy, lower alkanesulfonyloxy, such as methanesulfonyloxy, or more especially halogen, such as chlorine, bromine or iodine, leads to a compond of the formula XVII,

HO-Z''-Q* (XVII)

wherein Q* and Z'' are as defined for a compound of formula XV and XVI, respectively, the reaction conditions being analogous to those for reaction under process b) of a compound of formula IV with a compound of formula V.

Introduction of a nucleofugal leaving group A, e.g. by reaction of the hydroxy group with an arylsulfonylhalogenide or a lower alkanesulfonylhalogenide and, if desired, replacement of the resulting arylsulfonyloxy group or lower alkanesulfonyloxy group with a halogenide, leads then to a compound of formula III wherein Z is Z'' and Q is Q*, as defined in the last paragraph.

A compound of formula IV may, for example, be prepared by nucleophilic reaction of a compound of the formula II, as defined under process a), with a compound of the formula XVIII,

Z**-K (XVIII)

wherein Z** is as defined for Z' for a compound of formula IV, except that the bond to the nirtogen in formula IV is missing, and K is a nucleofugal leaving group, especially aryl-sulfonyloxy, such as toluenesulfonyloxy, lower alkanesulfonyloxy, such as methanesulfonyl-oxy, or more especially halogen, such as chlorine, bromine or iodine.

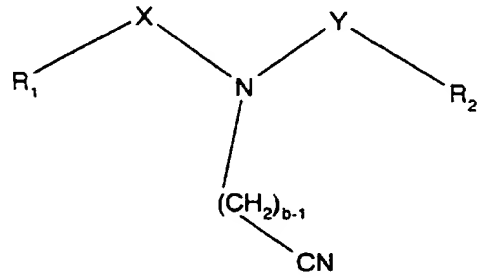
Alternatively, it is possible to proceed in analogy to the preparations given in the Examples, comprising reduction of a cyano precursor to the amino compound of formula IV (see also below for the synthesis of a compound of the formula VI).

A compound of the formula VI is known in the art or commercially available, and/or it can be synthesized according to the following proceedure:

Nucleophilic reaction of a compound of the formula II, as defined above, with a compound of the formula XIX

$$M\text{-}(CH_2)_{b-1}\text{-}CN \qquad (XIX)$$

wherein M is a nucleofugal leaving group, especially arylsulfonyloxy, such as toluene-sulfonyloxy, lower alkanesulfonyloxy, such as methanesulfonyloxy, or more especially halogen, such as chlorine (most preferred), bromine or iodine, and b is as defined for a compound of formula I, leads to a compound of the formula XX,



(XX)

wherein R_1, X, Y, R_2 and b are as defined under a compound of formula I, which can then be reduced to an amino compound of the formula VI, e.g. with hydrogen in the presence of a catalyst, such as Raney-Nickel, or with a complex hydride, such as lithium aluminium hydride ($LiAlH_4$).

Alternatively, a compound of the formula XIX*,

$$(CH_2{=}CH)\text{-}(CH_2)_{b-3}\text{-}CN \qquad XIX^*$$

wherein b has the meanings given in a compound of the formula I, being not less than 3, can be added to a compound of formula II, as defined above; subsequent reduction, as descibed above for compounds of formula XX, leads then to the corresponding amino compound of formula VI.

Unsubstituted or substituted 1,8-naphthalene-dicarboxylic acids (1,8-naphthalic acids) are known in the art or commercially available, or they can be prepared according to procedures that are known in the art (see, for example, DE-OS 28 23 987, DE-OS 23 23 555 and US 4,146,720.

General process conditions

The following applies in general to all processes mentioned hereinbefore and hereinafter:

Functional groups in starting materials the reaction of which is to be avoided, especially carboxy, amino, hydroxy, mercapto and sulfo groups, can be protected by suitable protecting groups (conventional protecting groups) which are customarily used in the synthesis of peptide compounds, and also in the synthesis of cephalosporins and penicillins as well as nucleic acid derivatives and sugars. These protecting groups may already be present in the precursors and are intended to protect the functional groups in question against undesired secondary reactions, such as acylation, etherification, esterification, oxidation, solvolysis, etc.. In certain cases the protecting groups can additionally cause the reactions to proceed selectively, for example stereo selectively. It is characteristic of protecting groups that they can be removed easily, i.e. without undesired secondary reactions taking place, for example by solvolysis, reduction, photolysis, and also enzymatically, for example also under physiological conditions, and, especially, that they are not present in the end products.

The protection of functional groups by such protecting groups, the protecting groups themselves and the reactions for their removal are described, for example, in standard works such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in Th. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides", Volume 3 (E. Gross and J. Meienhofer, eds.), Academic Press, London and New York 1981, in "Methoden der organischen Chemie", Houben-Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H.

Jescheit, "Aminosäuren, Peptide, Proteine" ("Amino acids, peptides, proteins"), Verlag Chemie, Weinheim, Deerfield Beach and Basle 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" ("The Chemistry of Carbohydrates: monosaccharides and derivatives"), Georg Thieme Verlag, Stuttgart 1974.

When several protected functional groups are present, if desired the protecting groups can be so selected that more than one such group can be removed simultaneously, for example by acidolysis, such as by treatment with trifluoro acetic acid, or with hydrogen and a hydrogenation catalyst, such as a palladium-on-carbon catalyst. Conversely, the groups can also be so selected that they cannot all be removed simultaneously, but rather in a desired sequence, the corresponding intermediates being obtained.

In view of the close relationship between the compounds of formulal and their salts and starting materials (starting materials and intermediates) in free form and in the form of their salts, any reference hereinbefore and hereinafter to a free compound or a salt thereof is to be understood as meaning also the corresponding salt or free compound, respectively, where appropriate and expedient.

All the above-mentioned process steps can be carried out under reaction conditions that are known per se, preferably those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, preferably solvents or diluents that are inert towards the reagents used and are solvents therefor, in the absence or presence of catalysts, condensation agents or neutralising agents, for example ion exchangers, such as cation exchangers, e.g. in the H^+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from approximately -100°C to approximately 190°C, preferably from approxi mately -80°C to approximately 150°C, for example at from -80 to -60°C, at room temperature, at from -20 to 40°C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mix

tures of isomers, for example racemates or mixtures of diastereoisomers, for example ana logously to the methods described under "Additional process steps".

The solvents from which those solvents that are suitable for any particular reaction may be selected include, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, or phenols, such as phenol, nitriles, such as aceto nitrile, halogenated hydrocarbons, such as methylene chloride, acid amides, such as dimethylformamide, bases, such as heterocyclic nitrogen bases, for example pyridine, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or iso pentane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallisation.

If necessary, protected starting materials may be used in all process steps and the protecting groups may be removed at suitable stages of the reaction.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ. In the process of the present invention there are preferably used those starting materials which result in the compounds of formulal described at the beginning as being especially valuable. Special preference is given to reaction conditions and processes of manufacture that are analogous to those mentioned in the Examples.

The remaining starting materials required for the synthesis of compounds of the formulae I, II, III, IV, V and VI and the other compounds mentioned can be synthesized according to methods that are known in the art, or they are known and/or commercially available.

Pharmaceutical compositions, the preparation thereof, and the use according to the invention of a compound of formula I and compositions comprising compounds of formula I as active ingredient

The present invention relates also to pharmaceutical compositions that comprise (preferably a novel) compound of formula I, a tautomer or a salt thereof, as active ingredient and that can be used especially in the treatment of a disease mentioned at the beginning. Special preference is given to compositions for enteral, such as nasal, buccal, rectal or, especially, oral, and parenteral, such as intravenous, intramuscular or subcutaneous, administration to warm-blooded animals, especially humans. The compositions comprise the active ingredient on its own or, preferably, together with a pharmaceutically acceptable carrier. The dose of active ingredient depends on the disease to be treated, and on the species, its age, weight and individual condition, on individual pharmacokinetic conditions, and on the mode of administration.

The invention relates also to pharmaceutical compositions comprising (preferably a novel) compound of formula I, a tautomer or a pharmaceutically acceptable salt thereof, for use in a method for the prophylactic or, especially, therapeutic treatment of the human or animal body, to a process for the preparation thereof, especially as compositions for the treatment of a retroviral infection in a warm-blooded animal that is responsive to the inhibition of the interaction of a transcriptional regulator with a retroviral response element, preferably a HIV-, such as HIV-1-, infection which is responsive to the inhibition of the interaction between Tat and TAR and/or Rev and RRE; and more specifically for the treatment of AIDS and its initial stages, such as ARDS, in ahuman), and to a method of treating the diseases mentioned above.

The invention relates also to processes for, and to the use of (preferably the novel) compounds of formula I in the preparation of pharmaceutical compositions that comprise compounds of formula I as active component (active ingredient).

Preferred as active ingredient is always a novel compound of formula I, as defined above.

The pharmacologically acceptable compounds of the present invention may be used, for example, for the preparation of pharmaceutical compositions that comprise an effective amount of the active ingredient together or in admixture with a significant amount of inorganic or organic, solid or liquid, pharmaceutically acceptable carriers.

Preference is given to a pharmaceutical composition that is suitable for administration to a warm-blooded animal, especially a human or a (e.g. commercially usable) mammal, suffering from a retroviral disease that is responsive to the inhibition of the interaction of a transcriptional regulator with a retroviral response element; preferably a HIV-infection, such as a HIV-1-infection, which is responsive to the inhibition of the interaction between Tat and TAR and/or Rev and RRE, and more specifically for the treatment of AIDS and its initial stages, such as ARDS, in a human; which composition comprises a compound of formula I, or a salt thereof where salt-forming groups are present, in an amount that is effective in inhibiting the interaction of transcriptional regulators with retroviral response elements, preferably of the interaction between Tat and TAR and/or Rev and RRE; together with at least one pharmaceutically acceptable carrier.

Preference is given also to a pharmaceutical composition for the prophylactic or, especially, therapeutic treatment of a retroviral infection in a warm-blooded animal that is responsive to the inhibition of the interaction of a transcriptional regulator with a retroviral response element, preferably a HIV-infection, such as a HIV-1-infection, which is responsive to the inhibition of the interaction between Tat and TAR and/or Rev and RRE; and more specifically for the treatment of AIDS and its initial stages, such as ARDS, in a warm-blooded animal, especially a human or a (e.g. commercially usable) mammal, which requires such treatment, especially because it is suffering from such a disease, which composition comprises as active ingredient a novel compound of formula I, or a pharma ceutically acceptable salt thereof, in an amount that is prophylactically or, especially, therapeutically effective against the mentioned diseases.

The pharmaceutical compositions comprise from approximately 1% to approximately 95% active ingredient, dosage forms that are in single dose form preferably comprising from

approximately 20% to approximately 90% active ingredient, and dosage forms that are not in single dose form preferably comprising from approximately 5% to approximately 20% active ingredient. Unit dose forms are, for example, dragées, tablets, ampoules, vials, suppositories or capsules. Other dosage forms are, for example, ointments, creams, pastes, foams, tinctures, lipsticks, drops, sprays, dispersions, etc.. Examples are capsules comprising from approximately 0.05g to approximately 1.0g of the active ingredient.

The pharmaceutical compositions of the present invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissol ving or lyophilising processes.

There are preferably used solutions of the active ingredient, additionally also suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions, which, for example in the case of lyophilised compositions comprising the active ingredient on its own or together with a carrier, e.g. mannitol, may be prepared before use. The pharmaceutical compositions may be sterilised and/or may comprise excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known per se, for example by means of conventional dissolving or lyophilising processes. The said solutions or suspensions may comprise viscosityincreasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin, or also solubilisers, for example ®Tween 80 [polyoxyethylene(20) sorbitan monooleate; trademark of ICI Americas, Inc, USA].

Suspensions in oil comprise as the oil component the vegetable, synthetic or semisynthetic oils customarily used for injection purposes. There may be mentioned especially liquid fatty acid esters which contain as acid component a long-chain fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid or linoleic acid, where appropriate with the addition of antioxidants, for example vitamin E, b-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of those fatty acid esters has not more than 6 carbon atoms and is a mono- or poly-valent, for example mono-, di- or tri-valent, alcohol, for example methanol, ethanol, propanol, butanol or pen-

tanol or their isomers, but especially glycol and glycerol. Accordingly, there may be mentioned as examples of fatty acid esters: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M2375" (polyoxyethylene glycerol trioleate from Gattefossé, Paris), "Labrafil M1944 CS" (unsaturated polyglycolised glycerides prepared by alcoholysis of apricot kernel oil and composed of glycerides and polyethylene glycol esters; Gattefossé, France), "Labrasol" (saturated polyglycolised glycerides prepared by alcoholysis of TCM and composed of glycerides and polyethylene glycol esters; Gattefossé, France) and/or "Miglyol812" (triglyceride of saturated fatty acids having a chain length of from C_8 to C_{12} from Hüls AG, Germany), but especially vegetable oils, such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and, more especially, groundnut oil.

The preparation of the injection compositions is carried out in customary manner under sterile conditions, as well as the introduction, for example, into ampoules or vials and the sealing of the containers.

Pharmaceutical compositions for oral administration can be obtained, for example, by combining the active ingredient with one or more solid carriers, granulating a resulting mixture, where appropriate, and processing the mixture or granules, if desired, where appropriate with the addition of additional excipients, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tri calcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches and also carboxymethyl starch, cross-linked polyvinylpyrrolidone, or alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Dragée cores can be provided with suitable, where appropriate enteric coatings, there being used inter alia concentrated sugar solutions, which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable

organic solvents or solvent mixtures or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Pharmaceutical compositions for oral administration are also hard gelatin capsules, and soft sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The hard gelatin capsules may comprise the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders and/or glidants, such as talc or magnesium stearate, and, where appropriate, stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene glycol or propylene glycol, it likewise being possible to add stabilisers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type.

Other oral dosage forms are, for example, syrups prepared in customary manner which comprise the active ingredient, for example, in suspended form and in a concentration of approximately from 5% to 20%, preferably approximately 10% or in a similar concentration that provides a suitable single dose when administered, for example, in a measure of 5 or 10ml. Also suitable are, for example, powdered or liquid concentrates for the preparation of shakes, for example in milk. Such concentrates may also be packed in single dose quantities.

Suitable rectally administrable pharmaceutical compositions are, for example, supposi tories that consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

For parenteral administration there are suitable, especially, aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, or aqueous injection suspensions that comprise viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilisers. The active ingredient, where appropriate together with excipients, can also be in the form of a lyophilisate

and be made into a solution prior to parenteral administration by the addition of suitable solvents.

Solutions used, for example, for parenteral administration can also be used as infusion solutions.

Preferred preservatives are, for example, antioxidants, such as ascorbic acid, or micro bicides, such as sorbic acid or benzoic acid.

Ointments are oil-in-water emulsions that comprise up to 70%, but preferably from 20 to 50%, water or aqueous phase. There are suitable as the fatty phase especially hydro carbons, for example paraffin oil or hard paraffins, which, in order to improve the water-binding capacity, preferably contain suitable hydroxy compounds, such as fatty alcohols or esters thereof, for example cetyl alcohol or wool wax alcohols, such as wool wax. Emulsifiers are corresponding lipophilic substances, such as sorbitan fatty acid esters, for example sorbitan oleate and/or sorbitan isostearate. Additives to the aqueous phase are, for example, humectants, such as polyalcohols, for example glycerol, propylene glycol, sorbitol and/or polyethylene glycol, or preservatives and perfumes.

Fatty ointments are anhydrous and comprise as base especially hydrocarbons, for example paraffin or paraffin oil, also natural or partially synthetic fats, for example coconut fatty acid triglyceride, or preferably hardened oils, for example hydrogenated groundnut oil or castor oil, also fatty acid partial esters of glycerol, for example glycerol mono- and/or di-stearate, and also, for example, the fatty alcohols increasing water absorption, emulsifiers and/or additives mentioned in connection with the ointments.

Creams are oil-in-water emulsions that comprise more than 50% water. As oily base there are used especially fatty alcohols, for example lauryl, cetyl or stearyl alcohol, fatty acids, for example palmitic or stearic acid, liquid to solid waxes, for example isopropyl myristate, wool wax or beeswax, and/or hydrocarbons, for example Vaseline® (petrolatum) or paraffin oil. Suitable emulsifiers are surface-active substances having predominantly hydrophilic properties, such as non-ionic emulsifiers, for example fatty acid esters of polyalcohols or ethylene oxide adducts thereof, such as polyglyceric acid fatty acid esters or polyethylene sorbitan fatty acid esters, and also polyoxyethylene fatty alcohol ethers or fatty acid esters, or cor-

responding ionic emulsifiers, such as alkali metal salts of fatty alcohol sulfates, for example sodium lauryl sulfate, sodium cetyl sulfate or sodium stearyl sulfate, which are usually used in the presence of fatty alcohols, for example cetyl alcohol or stearyl alcohol. Additives to the aqueous phase are inter alia agents that reduce the drying out of the creams, for example polyalcohols, such as glycerol, sorbitol, propylene glycol and/or polyethylene glycols, also preservatives and perfumes.

Pastes are creams and ointments having secretion-absorbing powder constituents, such as metal oxides, for example titanium oxide or zinc oxide, also talc and/or aluminium silicates, the purpose of which is to bind any moisture or secretions present.

Foams are administered from pressurised containers and are liquid oil-in-water emulsions in aerosol form, there being used as propellants halogenated hydrocarbons, such as chlorofluoro-lower alkanes, for example dichlorodifluoromethane and dichlorotetrafluoroethane, or preferably non-halogenated gaseous hydrocarbons, air, N_2O or carbon dioxide. As oil phase there are used inter alia the oil phases used above under ointments and creams, likewise the additives mentioned therein.

Tinctures and solutions generally have an aqueous-ethanolic base to which there are added inter alia polyalcohols, for example glycerol, glycols and/or polyethylene glycol, as humectants for reducing evaporation, and fat-restoring substances, such as fatty acid esters with low molecular weight polyethylene glycols, that is to say lipophilic substances that are soluble in the aqueous mixture, as a replacement for the fatty substances removed from the skin by the ethanol, and, if necessary, other excipients and additives.

The invention relates also to a process or a method for the treatment of a pathological condition mentioned above, especially a retroviral disease which is responsive to inhibition of the interaction of a transcriptional regulator with a retroviral response element, preferably a HIV-infection, such as a HIV-1-infection, which is responsive to the inhibition of the interaction between Tat and TAR and/or Rev and RRE; and more specifically for the treatment of AIDS and its initial stages, such as ARDS, in a human. The compounds of formula I may be administered prophylactically or therapeutically as such or in the form of pharmaceutical compositions, preferably in an amount that is effective against the mentioned diseases, to a warm-blooded animal, for example a human, requiring such treatment, the compounds

being used especially in the form of pharmaceutical compositions. In the case of a body weight of approximately 70kg, a daily dose of from approximately 0.1g to approximately 5g, preferably from approximately 0.5g to approximately 2g, of a compound of the present invention is administered.

The invention relates also to a pharmaceutical composition that is suitable for administration to a warm-blooded animal, especially a human (or to cells or cell lines derived from a warm-blooded animal, especially a human, e.g. lymphocytes), for the treatment or prevention of (= prophylaxis against) a disease that responds to inhibition of retroviral Tat/TAR interaction retroviral protease; especially inhibition of HIV, more preferably HIV-1, Tat/TAR interaction; for example a retroviral infection such as HIV infection, more especially AIDS, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, effective for the inhibition of the Tat/TAR interaction, especially for the treatment of HIV infection, together with at least one pharmaceutically acceptable carrier.

The pharmaceutical compositions according to the invention are those for enteral, such as nasal, rectal or oral, or parenteral, such as intramuscular or intravenous, administration to warm-blooded animals (humans and animals), that comprise an effective dose of the pharmacological active ingredient, alone or together with a significant amount of a pharmaceutically acceptable carrier. The dose of the active ingredient depends on the species of warm-blooded animal, the body weight, the age and the individual condition, individual pharmacokinetic data, the disease to be treated and the mode of administration.

The invention relates also to a method of treating (also for prophylaxis) a retroviral infection by inhibiting the interaction of a transcriptional regulator with a retroviral response element, for example HIV infection, including AIDS, which comprises administering a prophylactically or especially therapeutically effective amount of a compound of formula I according to the invention, especially to a warm-blooded animal, for example a human, who on account of at least one of the mentioned diseases, especially an HIV-infection, including AIDS, requires such treatment.

The dose to be administered to warm-blooded animals, for example humans of approximately 70 kg body weight, is from approximately 3 mg to approximately 3 g, preferably from approximately 10 mg to approximately 1.5 g, for example approximately

from 100 mg to 1000 mg per person per day, divided preferably into 1 to 3 single doses which may, for example, be of the same size. Usually, children receive half of the adult dose.

The pharmaceutical compositions comprise from approximately 1 % to approximately 95%, preferably from approximately 20 % to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, dragées, tablets or capsules.

The pharmaceutical compositions of the present invention are prepared in a manner known *per se*, for example by means of conventional dissolving, lyophilising, mixing, granulating or confectioning processes.

Solutions of the active ingredient, and also suspensions, and especially isotonic aqueous solutions or suspensions, are preferably used, it being possible, for example in the case of lyophilised compositions that comprise the active ingredient alone or together with a carrier, for example mannitol, for such solutions or suspensions to be produced prior to use. The pharmaceutical compositions may be sterilised and/or may comprise excipients, for example preservatives, stabilisers, wetting and/or emulsifying agents, solubilisers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known *per se*, for example by means of conventional dissolving or lyophilising processes. The said solutions or suspensions may comprise viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin.

Suspensions in oil comprise as the oil component the vegetable, synthetic or semi-synthetic oils customary for injection purposes. There may be mentioned as such especially liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brasidic acid or linoleic acid, if desired with the addition of anti oxidants, for example vitamin E, b-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of those fatty acid esters has a maximum of 6 carbon atoms and is a mono- or poly-hydric, for example a mono-, di- or tri-hydric, alcohol, for example methanol, ethanol, propanol, butanol

or pentanol or the isomers thereof, but especially glycol and glycerol. The following examples of fatty acid esters are therefore to be mentioned: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethylene glycerol trioleate, Gattefossé, Paris), "Miglyol 812" (triglyceride of saturated fatty acids with a chain length of C_8 to C_{12}, Hüls AG, Germany), but especially vegetable oils, such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

The injection compositions are prepared in customary manner under sterile conditions; the same applies also to introducing the compositions into ampoules or vials and sealing the containers.

Pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, dragée cores or capsules. It is also possible for them to be incorporated into plastics carriers that allow the active ingredients to diffuse or be released in measured amounts.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starch pastes using for example corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinyl pyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used, *inter alia*, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as ethylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Capsules are dry-filled capsules made of gelatin and soft sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may comprise the active ingredient in the form of granules, for example with fillers, such as

lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and if desired with stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable oily excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also for stabilisers and/or antibacterial agents to be added. Dyes or pigments may be added to the tablets or dragée coatings or the capsule casings, for example for identification purposes or to indicate different doses of active ingredient.

Examples

Embodiments of the invention are described in the following specific examples which are not to be construed to be intended to limit the scope of the invention in any way, but serve merely for illustration:

Temperatures, if not mentioned: room temperature or ambient temperature. In mixtures, relations of parts of solvent or eluent or reagent mixtures in liquid form are given as volume relations (v/v), if not indicated otherwise.

Special abbreviations used are:

Boc	tert-butoxycarbonyl
MeOH	methanol
m.p.	melting point
R_F	ratio of fronts in thin layer chromatography
R_t	retention time in HPLC (min)
TFA	trifluoroacetic acid
THF	tetrahydrofurane

Described compounds can be synthesized according to methods outlined within this specification, especially in analogy to the methods decribed in Examples 1, 2 and 8. Silica gel (mean diameter 40-63 mm from E. Merck, Darmstadt, FRG is used for flash chromatography.

For thin layer chromatography, Silica gel 60 F 254 plates from E. Merck, Darmstadt, FRG, are used. Solvent System A for thin layer chromatography has the following composition: chloroform/methanol/25 NH_3 in water/water (4:4:1.36:0.64).

Theoretical values for Elemental Analysis are given in parenthesis behind the values obtained, respectively.

For HPLC, the retention time is determined using a 4 x 250 mm C18 reversed-phase column (classified as 5µ beads with 10 nm pores: Macherey & Nagel, Düren, FRG) with a flow rate of 1 ml/min and UV detection at 280 nm and a gradient of 5%B in A -> 100 %B in 15 min (A = 0.1 % TFA in water, B = 0.1 % TFA in acetonitrile).

For mixtures of solvents and eluents, ratios of the components are given with reference to volumes (v/v).

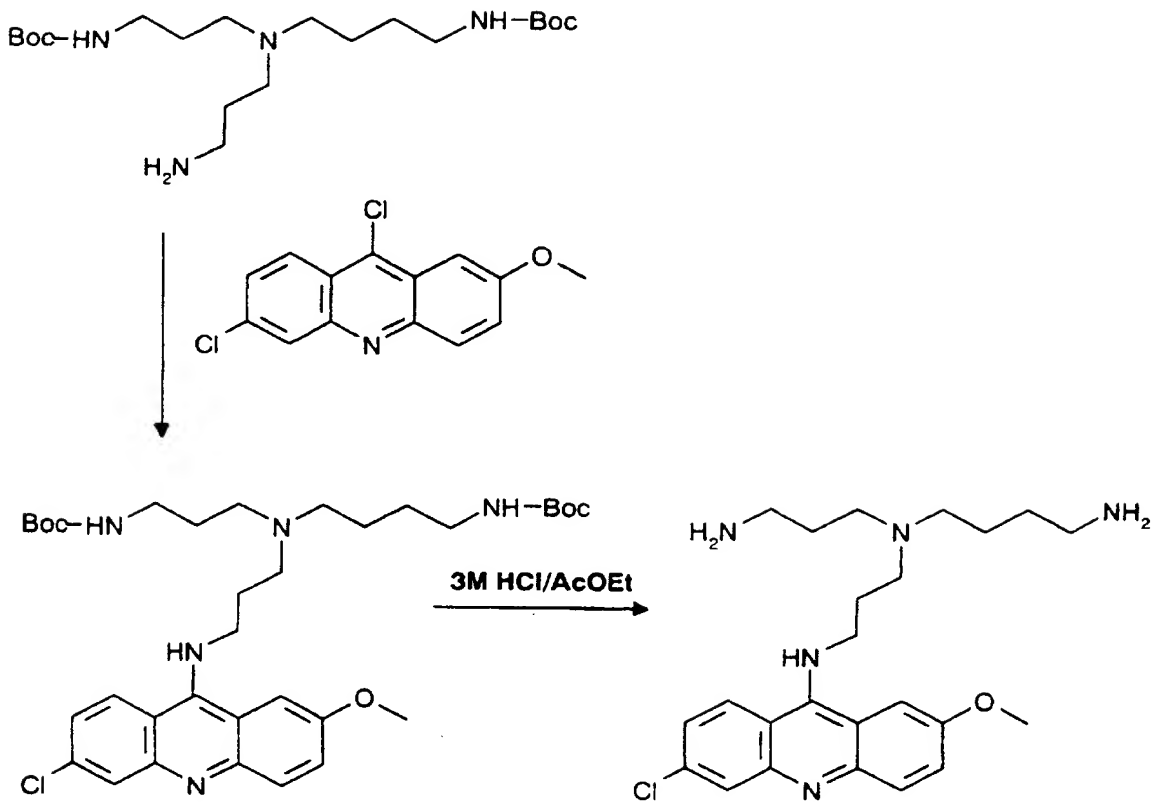
Example 1: 5-(3-{6-Chloro-2-methoxy-acridin-9-yl}-aminopropyl)-1,5,10-triazadecane tetrahydrochloride

40 ml 3M HCl in ethyl acetate is added to a solution of 10.8 g (17 mmol) of the title compound of Example 1b) in 40 ml of ethyl acetate at 10 °C. The reaction mixture is stirred at room temperature for 1 hour. The precipitating yellow crystals are filtered off, washed with ethyl acetate and dissolved under heating in 150 ml of methanol and a few drops of water. The solution is treated with activated charcoal and filtrated over Hyflo Super Cel® (diatomaceous earth, obtainable from Fluka, Buchs, Switzerland) and cooled down to 0 °C. The precipitating product is filtered off and recrystallized from methanol/ethyl acetate giving yellow crystals (m.p. 242 °C).

Elemental analysis: $C_{24}H_{34}ClN_5O \times 4HCl \times 1.1\ H_2O$

C: 47.9 (47.3), H: 6.8 (6.6), Cl: 29.1 (29.1), N: 11.7 (11.5), H_2O: 3.7 (3.3)

Synthesis Scheme:



The starting materials are prepared as follows:

1a) 5-(3-Aminopropyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane

The title compound is synthesized according to the procedure of G.M. Cohen et al. (see J. Chem. Soc. Chem. Commun., 298-300 (1992)) starting with the reaction of 1,10-di-tert-butoxycarbonyl-1,5,10-triazadecane (N,N'-bis-Boc-spermidine) and acrylonitrile followed by hydrogenation with hydrogen in the presence of Raney nickel.

R_F = 0.23 (CH_2Cl_2/MeOH/30% NH_3 = 40:10:1

1b) 5-(3-(6-Chloro-2-methoxy-acridin-9-yl)-aminopropyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane

8.05 g (20 mmol) of the title compound of Example 1a) I and 5.56 g (20 mmol) of 6,9-dichloro-2-methoxyacridine (Aldrich, Buchs, Switzerland) are dissolved in 10 g of phenol at 110 °C under nitrogen. After 1 hour, the reaction mixture is cooled to room temperature and the product is purified by flash chromatography (methylene chloride/methanol = 20:1 -> 4:1) giving a yellow oil (R_F = 0.25, methylene chloride/MeOH = 9:1)..

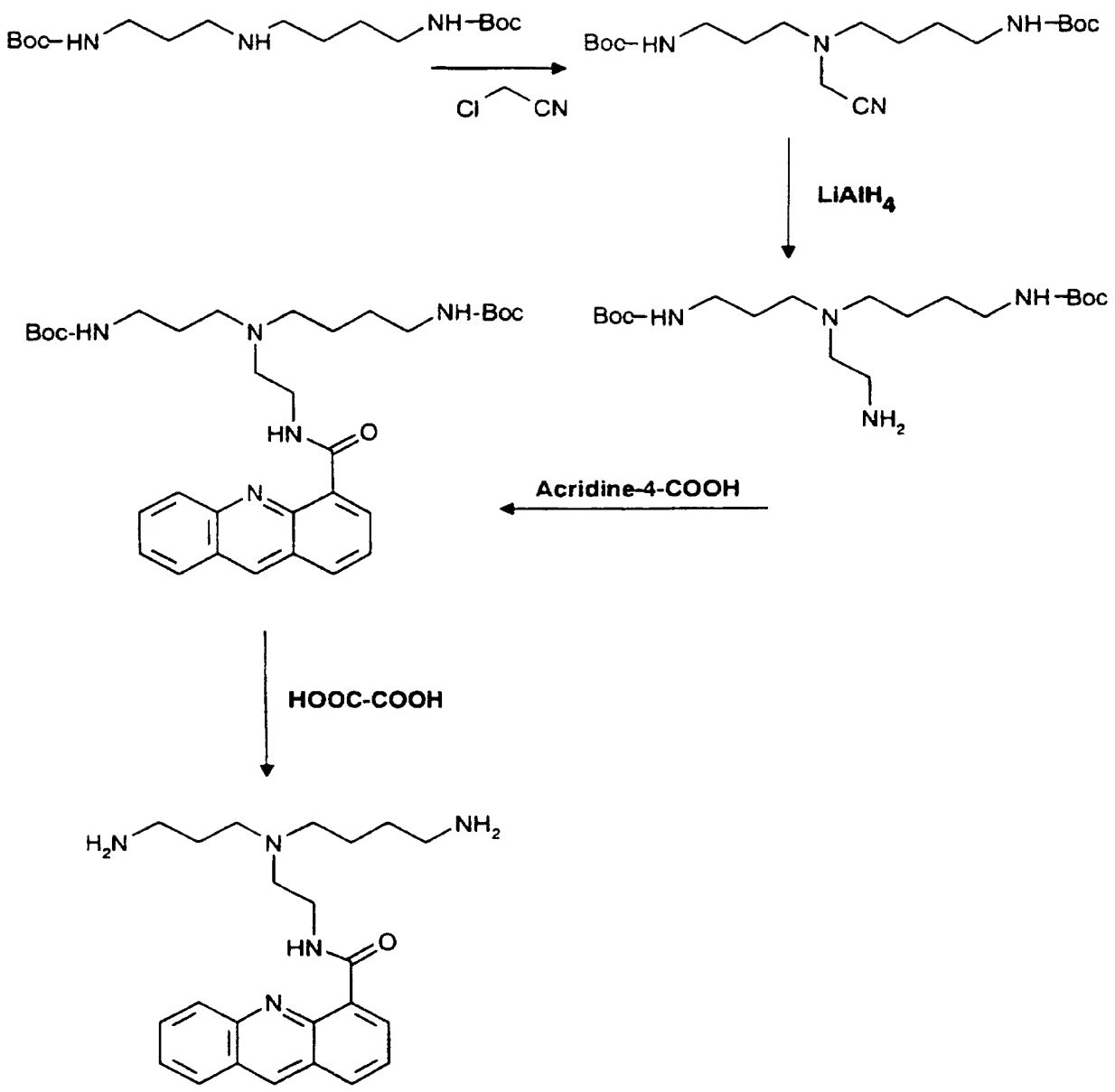
Example 2: 5-(2-{4-Acridinoyl}-aminoethyl)-1,5,10-triazadecane

1.13 g (1.9 mmol) of 5-(2-{4-acridinoyl}-aminoethyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane and 971 mg (7.7 mmol) of oxalic acid (dihydrate) are refluxed in 30 ml of 50% aqueous methanol for 23 hours. The solvent is evaporated under vacuum and the crude product is recrystallized from water/methanol. The solid is dried at 100 °C under vacuum giving the title compound in the form of crystals (m.p. 126-132°C).

Elemental analysis: $C_{23}H_{31}N_5O \times 3\ C_2H_2O_4 \times H_2O$

C: 51.3 (51.1), H: 5.7 (5.8), N: 10.3 (10.3), H_2O: 2.6 (2.6).

Synthesis Scheme:



The starting materials are prepared as follows:

2a) 5-(2-(4-Acridinoyl)-aminoethyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane

1.94 g (5 mmol) of 5-(2-aminoethyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane, 1.1 g (5 mmol) of acridine-4-carboxylic acid, 0.77 g (5 mmol) of hydroxybenzotriazole, and 1.14 g (5.5 mmol) of dicyclohexylcarbodiimide are dissolved in 10 ml of THF at -5 °C and stirred at roorn temperature for 20 hours. The precipitated dicyclohexyl urea is filtered off, and the filtrate is concentrated under reduced pressure, taken up in ethyl acetate, washed two times with $NaHCO_3$-solution and dried over Na_2SO_4; then the solvent is removed under reduced

pressure.The resulting oil is purified by flash chromatography (methylene chloride/methanol = 99:1 -> 9:1) giving the title compound as an oily product (R_F = 0.33, methylene chloride/MeOH = 9:1).

2b) 5-(2-Aminoethyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane

To a solution of 6 g (15.6 mmol) 5-cyanomethyl-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane in diethyl ether, 1.78 g (47 mmol) of $LiAlH_4$ is added in portions at 0-5 °C. The reaction mixture is stirred at room temperature during 2 hours under nitrogen atmosphere. Under cooling at 0-5 °C, 4.84 ml (36.8 mmol) of triethanolamine is added slowly, and the reaction mixture is stirred for additional 10 minutes.Then, under cooling, 2.0 ml (111 mmol) of water is added during 10 minutes and the reaction mixture is stirred at room temperature for 16 hours. The resulting grey suspension is filtered and the volatile components are removed under vacuum giving the title compound as a pale yellow oil (R_F = 0.37, methylene chloride/MeOH/30% aqueous NH_3 = 40:10:1).

2c) 5-Cyanomethyl-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane

A suspension of 6.9 g (20 mmol) of 1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane (= N,N'-bis-Boc-spermidine - see G.M. Cohen et al., J. Chem. Soc. Chem. Commun., 298-300 (1992)), 1.52 ml (24 mmol) of chloroacetonitril (Fluka, Buchs, Switzerland) and 22.1 g (160 mmol) of K_2CO_3 in 70 ml of acetonitrile is refluxed for 8 hours. After that, 0.34 ml (5.4 mmol) of chloroacetonitrile and 4.42 g (32 mmol) of K_2CO_3 are added and the reaction mixture is refluxed again for three hours. After filtration and concentration under vacuum, the crude product is purified by flash chromatography (methylene chloride -> methylene chloride/methanol: 19:1) giving the title compound as a brown oil (R_F = 0.76, methylene chloride/MeOH = 9:1).

2d) Acridine-4-carboxylic acid

The title compound is synthesized starting from 2-[(o-carboxyphenyl)amino]-benzaldehyde according to the procedure of G.J. Atwell et al. (see J. Med. Chem. 30, 664-9 (1987)); m.p. 192-3 °C; light brown crystals.

Example 3: N-(3-[1,5,10-Triazadecan-5-yl]-propyl)-3-nitro-1,8-naphthalimide trihydrochloride

The title compound is prepared in analogy to that of Example 8, starting from 1,8-naphthalic anhydride (Fluka, Buchs, Switzerland) and 5-(3-aminopropyl)-1,10-di-(tert-butoxycarbonyl)-

1,5,10-triazadecane (Example 1a). R_F = 0.26 (CH_2Cl_2/MeOH/30% NH_3 = 10:3.5:1; decomposition point 193-195 °C.

Example 4: 5-(3-{7-Nitro-benzo-2-oxa-1,3-diazol-4-yl}-aminopropyl)-1,5,10-triazadecane tetrahydrochloride

The title compound is prepared in analogy to that of Example 1, starting from 4-chloro-7-nitro-benzo-2-oxa-1,3-diazol (= 4-chloro-7-nitro-benzofurazan; Fluka, Buchs, Switzerland) and 5-(3-aminopropyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane (Example 1a), giving the title compound as an oil, R_F= 0.55 ($CHCl_3$/MeOH/25% NH_3/H_2O = 4:4:1.36:0.64; R_t (HPLC) = 7.76 min.

Example 5: 5-(2-{7-Nitro-benzo-2-oxa-1,3-diazol-4-yl }-aminoethpyl)-1,5,10-triazadecane tetrahydrochloride

The title compound is prepared in analogy to that of Example 1 starting from 4-chloro-7-nitro-benzo-2-oxa-1,3-diazol (= 4-chloro-7-nitro-benzofurazan; Fluka, Buchs, Switzerland) and 5-(2-aminoethyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane (Example 2b)), giving the title compound in the form of an oil: R_F= 0.56 (system A), R_t = 8 min.

Example 6: N-(2-[1,5,10-Triazadecan-5-yl]-ethyl)-1,8-naphthalimide trihydrochloride

The title compound is prepared in analogy to that of Example 8 starting from 1,8-naphthalic anhydride (Fluka, Buchs, Switzerland) and 5-(2-aminoethyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane (Example 2b), m.p. 254-256 °C, R_F = 0.68 (system A).

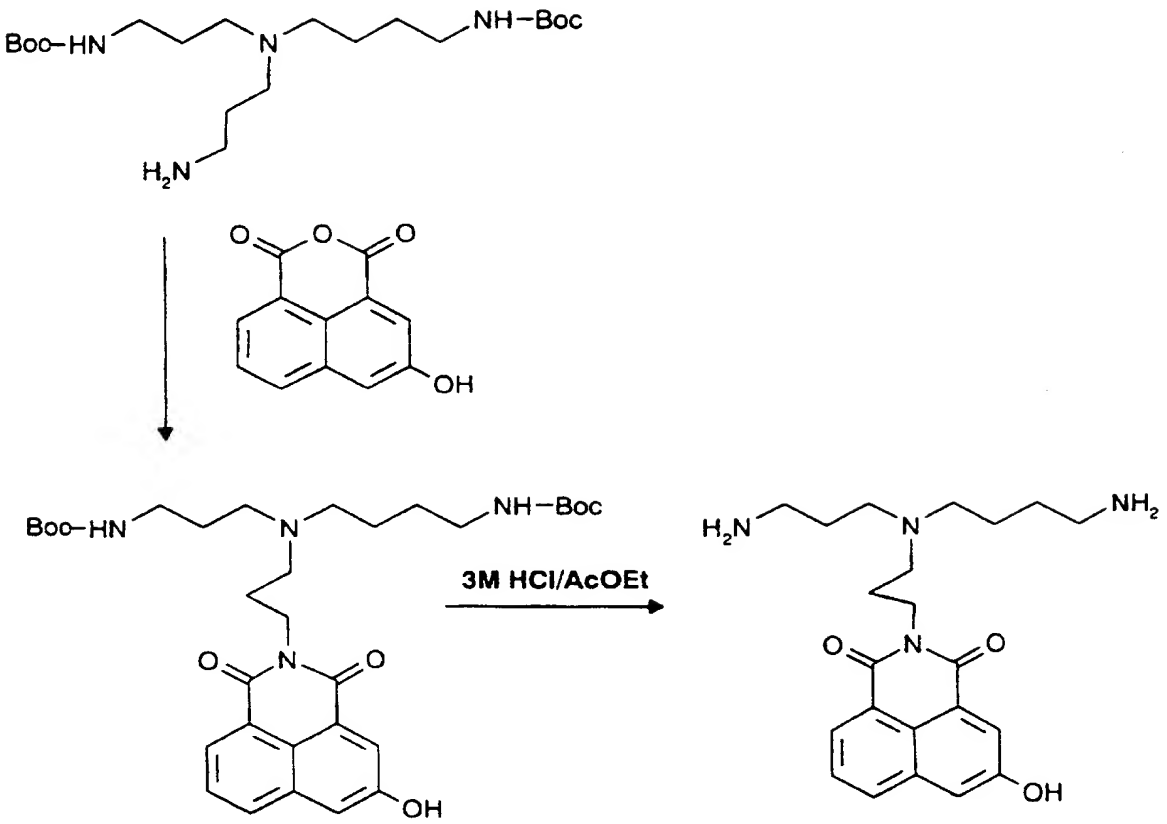
Example 7: N-(3-[1,5,10-Triazadecan-5-yl]-propyl)-1,8-naphthalimide trihydrochloride

The title compound is prepared in analogy to that of Example 8 starting from 1,8-naphthalic anhydride (Fluka, Buchs, Switzerland) and 5-(3-aminopropyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane (Example 1a), m.p. = 251-259 °C, R_F = 0.68 (system A).

Example 8: N-(3-[1,5,10-Triazadecan-5-yl]-propyl)-3-hydroxy-1,8-naphthalimide trihydrochloride

1.63 g (1.93 mmol) of N-(3-[1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecan-5-yl]-propyl)-3-hydroxy-1,8-naphthalimide is deprotected in analogy to Example 1) giving the title compound in the form of a white powder (m.p. 258-260°C; R_F = 0.5, $CHCl_3$/MeOH/25% NH_3/water = 4:4:1.36:0.64).

Synthesis Scheme:



The starting material is prepared as follows:

8a) N-(3-[1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecan-5-yl]-propyl)-3-hydroxy-1,8-naphthalimide

2 g (5 mmol) of 5-(3-aminopropyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane (Example 1a)) and 1.07 g (5mmol) of 3-hydroxy-1,8-naphthalic anhydride (TCI, Tokyo Kasei, Japan) are stirred in 50 ml of isopropanol at room temperature over night. After evaporating the solvent, the crude product is purified by means of flash chromatography (methylene chloride/MeOH = 95:5) giving the title compound in the form of a white powder (R_F = 0.15 with methylene chloride/MeOH = 95:5).

Example 9: N-(3-[1,5,10-Triazadecan-5-yl]-propyl)-4-chloro-1,8-naphthalimide trihydrochloride

The title compound is prepared in analogy to that of Example 8 starting from 4-chloro-1,8-naphthalic anhydride (Aldrich, Buchs, Switzerland) and 5-(3-aminopropyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane (Example 1a), giving the title compound as an oil:.R_F=0.69 (system A), R_t = 9.2 min.

Example 10: N-(2-[1,5,10-Triazadecan-5-yl]-ethyl)-3-hydroxy-1,8-naphthalimide trihydrochloride

The title compound is prepared in analogy to that of Example 8 starting from 3-hydroxy-1,8-naphthalic anhydride (TCI, Tokyo Kasei, Japan) and 5-(2-aminoethyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane (Example 2b): m.p. = 275-279 °C, R_F= 0.56 (system A).

Example 11: 5-(3-{Acridin-9-ylcarbonyl}-aminopropyl)-1,5,10-triazadecane tetrahydrochloride

The title compound is prepared in analogy to that of Example 2 starting from acridin-9-carbonic acid (Fluka, Buchs, Switzerland) and 5-(3-aminopropyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane (Example 1a): decomposition point = 140 °C, R_F = 0.63 (system A).

Example 12: 5-(2-{Acridin-9-ylcarbonyl}-aminoethyl)-1,5,10-triazadecane tetrahydrochloride

The title compound is prepared in analogy to that of Example 2 starting from acridine-9-carbonic acid (Fluka, Buchs, Switzerland) and 5-(2-aminoethyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane (Example 2b): m.p. 195 - 204 °C, R_F = 0.67 (system A).

Example 13: 5-(3-{2-Chloro-purin-6-yl}-aminopropyl)-1,5,10-triazadecane tetrahydrochloride

The title compound is prepared in analogy to that of Example 1 starting from 2,6-dichloro-purine (Aldrich, Buchs, Switzerland) and 5-(2-aminopropyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane (Example 1a)), giving the title compound as an oil: R_F = 0.39 (system A), R_t = 6.2 min.

Example 14: 5-(3-{6-Chloro-2-methoxy-acridin-9-yl}-aminopropyl)-1,5,9-triazanonane tetrahydrochloride

The title compound is prepared in analogy to that of Example 1, starting from 6,9-dichloro-2-methoxyacridine (Aldrich, Buchs, Switzerland) and 5-(3-aminopropyl)-1,9-di-(tert-butoxycarbonyl)-1,5,9-triazanonane (prepared in analogy to Example 1a starting from bis-(3-

aminopropylamine (Fluka, Buchs, Switzerland) and acrylonitrile): m.p. 246-250 °C, R_F= 0.71 (system A).

Example 15: 6-(3-{6-Chloro-2-methoxy-acridin-9-yl}-aminopropyl)-1,6,11-triazaundecane tetrahydrochloride

The title compound is prepared in analogy to that of Example 1, starting from 6,9-dichloro-2-methoxyacridine (Aldrich, Buchs, Switzerland) and 1,11-di-(tert-butoxycarbonyl)-1,6,11-triazaundecane (see Bergeron et al., Synthesis 9, 732-3 (1981)): m.p. = 232-240 °C, R_F= 0.73 (system A).

Example 16: 5-(4-{6-Chloro-2-methoxy-acridin-9-yl}-aminobutyl)-1,5,10-triazadecane tetrahydrochloride

The title compound is prepared in analogy to that of Example 1, starting from 6,9-dichloro-2-methoxyacridine (Aldrich, Buchs, Switzerland) and 5-(4-aminobutyl)-1,10-di-(tert-butoxy-carbonyl)-1,5,10-triazadecane: m.p. = 253-258 °C, R_F = 0.71 (system A)

The starting materials are prepared as follows:

16a) 5-(3-Cyanopropyl)-1,10-di(tert-butoxycarbonyl)-1,5,10-triazadecane

A mixture of 6.55 g (0.019 mol) of 1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane (see example 1), 2.2 g (0.021 mol) of sodium carbonate, 0.7 g (0.00475 mol) of potassium iodide and 2.35 g (0.0227 mol) of 4-chlorobutyronitrile (aldrich, Buchs, Switzerland) in 60 ml of 1-butanol is heated under reflux for 48 h. The reaction mixture is cooled to room temperature, filtered and concentrated under vacuum giving the title compound in the form of a yellow oil: R_F= 0.86 (CH_2Cl_2/MeOH/NH_3 25% = 40:10:1).

16b) 5-(4-Aminobutyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane

To a solution of 2.47 g (0.006 mol) of the title compound of example 16a) in 50 ml of diethyl ether, 1.15 g (0.03 mol) of $LiAlH_3$ is added in portions during 20 min. After stirring at room temperature for 5 h, 4 ml (0.03 mol) of triethanolamine is added. After stirring for 15 min, the solution is cooled down to 5 °C, and 1.08 ml (0.06 mol) of water is added. The grey suspension is stirred overnight at room temperature, filtered and concentrated under vacuum giving the title compound as a colourless oil: R_F= 0.16 (CH_2Cl_2/MeOH/NH_3 25% = 40:10:1).

Example 17: 5-(2-{6-Chloro-2-methoxy-acridin-9-yl}-aminoethyl)-1,5,10-triazadecane tetrahydrochloride

The title compound is prepared in analogy to that of Example 1, starting from 6,9-dichloro-2-methoxyacridine (Aldrich, Buchs, Switzerland) and 5-(2-aminoethyl)-1,10-di-(tert-butoxy-carbonyl)-1,5,10-triazadecane (Example 2b)): m.p. 195-220 °C, R_F = 0.77 (system A).

Example 18: 4-(2-{Acridin-9-ylcarbonyl}-aminoethyl)-1,4,7-triazaheptane trihydrochloride

The title compound is prepared in analogy to that of Example 2 starting from acridine-9-carbonic acid (Fluka, Buchs, Switzerland) and 4-(2-aminoethyl)-1,7-di-(tert-butoxycarbonyl)-1,4,7-triazaheptane (see Example 24 a):Decomposition point: 210 °C, R_F = 0.60 (system A), R_t= 6.88 min.

Example 19: 5-(p-{6-Chloro-2-methoxy-acridin-9-yl-aminomethyl}-benzyl)-1,5,10-triazadecane tetrahydrochloride

The title compound is prepared in analogy to that of Example 1 starting from 6,9-dichloro-2-methoxyacridine (Aldrich, Buchs, Switzerland) and 5-(p-aminomethylbenzyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane: Decomposition point = 192 °C, R_F= 0.77 (system A), R_t = 8.78 min.

The starting material is prepared as follows:

19a) 5-(p-Aminomethylbenzyl)-1,10-di-(tert-butoxycarbony)-1,5,10-triazadecane

The title compound is prepared in analogy to Example 2b) and 2c) starting from 1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane and 4-bromomethyl-benzonitrile (Fluka, Buchs, Switzerland).

Example 20: 6-(2-{6-Chloro-2-methoxy-acridin-9-yl}-aminoethyl)-1,6,11-triazaundecane tetrahydrochloride

The title compound is prepared in analogy to that of Example 1 starting from 6,9-dichloro-2-methoxyacridine (Aldrich, Buchs, Switzerland) and. 6-(2-aminoethyl)-1,11-di-(tert-butoxy-carbonyl)-1,6,11-triazaundecane (synthesized from 1,11-di-(tert-butoxycarbonyl)-1,6,11-triazaundecane (see Bergeron et al., Synthesis 9, 732-3 (1981)) and 2-chloroacetonitrile in analogy to Example 2b) and 2c): m.p. 237-245 °C, R_F = 0.8 (system A), R_t = 8.36 min.

Example 21: 8-(3-{6-Chloro-2-methoxy-acridin-9-yl}-aminopropyl)-1,8,15-triazapentadecane tetrahydrochloride

The title compound is prepared in analogy to that of Example 1 starting from 6,9-dichloro-2-methoxyacridine (Aldrich, Buchs, Switzerland) and 8-(2-aminopropyl)-1,15-di-(tert-butoxy-carbonyl)-1,8,15-triazapentadecane (prepared from bis-(6-aminohexyl)amine (Aldrich, Buchs, Switzerland) in analogy to the title compound of Example 2b): Decomposition point 192 °C, R_F= 0.77 (system A), R_t= 8.78 min.

Example 22: 5-(4-{6-Chloro-2-methoxy-acridin-9-yl}-aminobutyl)-1,5,9-triazanonane tetra-hydrochloride

The title compound is prepared in analogy to that of Example 1, starting from 6,9-dichloro-2-methoxyacridine (Aldrich, Buchs, Switzerland) and 5-(3-aminopropyl)-1,9-di-(tert-butoxycarbonyl)-1,5,9-triazanonane (prepared in analogy to Example 1a starting from bis-(3-aminopropylamine (Fluka, Buchs, Switzerland) and acrylonitrile): Decomposition point: 240 °C, R_F= 0.69 (system A), R_t= 8.57 min.

Example 23: 6-(4-{6-Chloro-2-methoxy-acridin-9-yl}-aminobutyl)-1,6,11-triazaundecane tetrahydrochloride

The title compound is prepared in analogy to that of Example 1, starting from 6,9-dichloro-2-methoxyacridine (Aldrich, Buchs, Switzerland) and 5-(4-aminobutyl)-1,10-di-(tert-butoxy-carbonyl)-1,5,10-triazaundecane: m.p. = 244-250 °C, R_F= 0.71 (system A), R_t= 8.75 min.

The starting material is prepared as follows:

23a) 5-(4-Aminobutyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazaundecane

The title compound is prepared in analogy to Example 16 a) and b) starting from 1,11-di(tert-butoxycarbonyl)-1,6,11-triazaundecane (see Example 15) and 4-chlorobutyronitrile (Fluka, Buchs, Switzerland).

Example 24: 4-(2-{6-Chloro-2-methoxy-acridin-9-yl}-aminoethyl)-1,4,7-triazaheptane tetrahydrochloride

The title compound is prepared in analogy to that of Example 1, starting from 6,9-dichloro-2-methoxyacridine (Aldrich, Buchs, Switzerland) and and 4-(2-aminoethyl)-1,7-di-(tert-butoxy-carbonyl)-1,4,7-triazaheptane: Decomposition point 210 °C, R_F= 0.79 (system A),

R_t= 8.69 min.

The starting material is prepared as follows:

24a) 4-(2-Aminoethyl)-1,7-di-(tert-butoxycarbonyl)-1,4,7-triazaheptane

A solution of 12.3 g (0.05 mol) of 2-(tert-butoxycarbonyl-oximino)-2-phemylacetonitrile (Fluka, Buchs, Switzerland) in 35 ml of THF is added to a solution of 3.65 g (0.025 mol) of tris(2-aminoethyl)amine (Fluka, Buchs, Switzerland) at 0 - 5 °C during 2 h. After stirring the reaction solution at room temperature overnight, the solvent is evaporated under reduced pressure, 80 ml of diethyl ether and 50 ml of water are added and the resulting suspension is adjusted to pH 3.0 by means of concentrated HCl. The aqueous phase is washed three times with 80 ml of diethyl ether and the combined ether phases are washed tice with 50 ml of water. After that, the water phases are combined, adjusted to pH 10 by means of 4N sodium hydroxide solution, and they are extracted three times with 50 ml of diethyl ether. These ether extracts are then combined and washed twice with 20 ml of water and once with 20 ml of brine and dried over sodium sulfate. The solvent is then evaporated under reduced pressure, giving the title compound as a colourless oil, R_F= 0.43 (CH_2Cl_2/MeOH/NH_3 25% = 40:10:1).

Example 25: 5-(5-{6-Chloro-2-methoxy-acridin-9-yl}-aminopentyl)-1,5,10-triazadecane tetrahydrochloride

The title compound is prepared in analogy to Example 1 starting from 6,9-dichloro-2-methoxyacridine and 5-(5-aminopentyl)-1,10-di-(tert-butoxycarbonyl)-1,5,10-triazadecane and has the following physical data: decomposition point 240 °C, R_F = 0.73 (solvent system A).

The starting material is prepared as follows:

25 a) 5-(5-Aminopentyl)-1,10-di(tert-butoxycarbonyl)-1,5,10-triazadecane

The title compound is prepared in analogy to Example 1a): R_F = 0.17 (CH_2Cl_2/MeOH/25%NH_3 = 40:10:1).

Example 26: 6-(4-{6-Chloro-2-methoxy-acridin-9-yl}-aminopentyl)-1,6,11-triazaundecane tetrahydrochloride

The title compound is prepared in analogy to Example 1 by starting from 6,9-dichloro-2-methoxyacridine and 5-(5-aminopentyl)-1,11-di-(tert-butoxycarbonyl)-1,6,11-triazaundecane: decomposition point 240 °C, R_F= 0.75 (solvent system A), R_t= 8.9 min.

The starting material is prepared as follows:

26 a) 5-(5-Aminopentyl)-1,11-di-(tert-butoxycarbonyl)-1,6,11-triazaundecane

The title compound is prepared in analogy to Example 1a) starting from 1,11-(di-tert-butoxy carbonyl)-1,6,11-triazaundecane (see Bergeron et al., Synthesis 9, 732-3 (1981)): R_F = 0.18 (CH_2Cl_2/MeOH/25%NH_3 = 40:10:1).

Example 27: Competition Tat-TAR gel-shift assay:

By the competition Tat-TAR gel-shift assay, the following IC_{50} values can be obtained with the following compounds:

Compound of Example	IC_{50} (nM)
1	12
2	21
3	34
6	50
8	50
9	75
10	40
14	50
15	40
16	50
17	25
25	25
26	45

Example 26: Gelatine solution:

A sterile-filtered aqueous solution, with 20 % cyclodextrins as solubilisers, of one of the compounds of formula I mentioned in the preceding Examples (e.g. Example 1) as active

ingredient, is so mixed under aseptic conditions, with heating, with a sterile gelatine solution containing phenol as preservative, that 1.0ml of solution has the following composition:

active ingredient 3 mg
gelatine 150.0 mg
phenol 4.7 mg
dist. water with 20 % cyclodextrins
as solubilisers 1.0 ml

Example 27: Sterile dry substance for injection:

5 mg of one of the compounds of formula I mentioned in the preceding Examples (e.g. Example 1) as active ingredient are dissolved in 1 ml of an aqueous solution with 20 mg of mannitol and 20 % cyclodextrins as solubilisers. The solution is sterile-filtered and introduced under aseptic conditions into a 2 ml ampoule, deep-frozen and lyophilised. Before use, the lyophilisate is dissolved in 1 ml of distilled water or 1 ml of a physiological saline solution. The solution is administered intramuscularly or intravenously. This formulation can also be introduced into a twin-chambered injection ampoule.

Example 28: Nasal spray:

500 mg of finely ground (<5.0 mm) powder of one of the compounds of formula I men tioned in the preceding Examples (e.g. Example 1) is suspended as active ingredient in a mixture of 3.5ml of Myglyol 812® and 0.08 g of benzyl alcohol. The suspension is introduced into a container having a metering valve. 5.0 g of Freon 12/ are introduced under pressure into the container through the valve. The "Freon" is dissolved in the Myglyol/benzyl alcohol mixture by shaking. The spray container contains approximately 100 single doses which can be administered individually.

Example 29: Film-coated tablets

The following ingredients are used for the preparation of 10000 tablets each containing 100 mg of active ingredient:

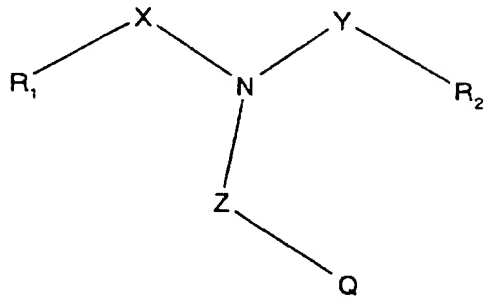
active ingredient 1000 g
corn starch 680 g

colloidal silica 200 g
magnesium stearate 20 g
stearic acid 50 g
sodium carboxymethyl starch 250 g
water quantum satis

A mixture of one of the compounds of formula I mentioned in the preceding Examples (e.g. Example 1) as active ingredient, 50 g of corn starch and the colloidal silica is processed with a starch paste, made from 250 g of corn starch and 2.2 kg of demineralised water, to form a moist mass. This is forced through a sieve having a mesh size of 3 mm and dried at 45° for 30min in a fluidised bed drier. The dry granules are pressed through a sieve having a mesh size of 1 mm, mixed with a pre-sieved mixture (1 mm sieve) of 330 g of corn starch, the magnesium stearate, the stearic acid and the sodium carboxymethyl starch, and compressed to form slightly biconvex tablets.

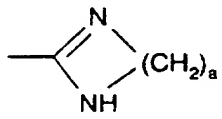
What is claimed is

1. The use of a compound of the formula I,

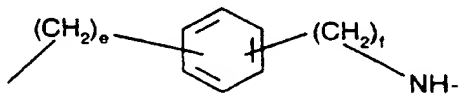
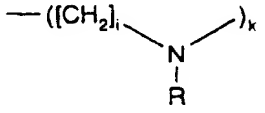


(I)

wherein

R_1 and R_2 are, independently of each other, a basic group selected from amino, N-alkylamino, N,N-dialkylamino, cycloalkylamino, amidino, N-lower alkylamidino, N,N-di-lower alkylamidino, guanidino, N-lower alkylguanidino, N,N-di-lower alkylguanidino and a group of the formula  ;

X and Y are a bivalent radical independently selected from the group consisting of $-(CH_2)_b-$, $-CH_2-(CH=CH-)_cCH_2-$, $-CH_2-(C\equiv C-)_dCH_2-$ and $-(CH_2)_g$-Cycloalkylen-$(CH_2)_h-$,

Z is, independently of X and Y, $-(CH_2)_b-$ or is a bivalent radical of the formula  or of the formula  , wherein R is hydrogen or lower alkyl, said bivalent radical being bound via its $-(CH_2)_e-$ or $-(CH_2)_i-$ to the nitrogen and via its -NH- or -N(R)- to Q in formula I,

Q is selected from aryl, arylcarbonyl, arylaminocarbonyl, heterocyclyl, heterocyclylcarbonyl or heterocyclylaminocarbonyl, aryl or heterocyclyl whenever mentioned containing 2 or more annelated rings,

a is 2 to 4,

b is 2 to 7,

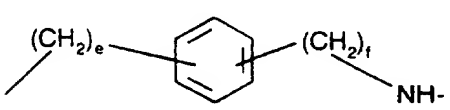
c, d, e and f is 1 to 3, respectively,

g and h is 0 to 3, respectively,

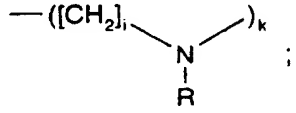
i is 2 to 7 and

k is 1 to 3,

with the proviso that Q is arylcarbonyl, arylaminocarbonyl, heterocyclylcarbonyl or heterocyclylaminocarbonyl only if Z is a bivalent radical of the formula



or



;

a tautomer thereof, or a salt thereof,

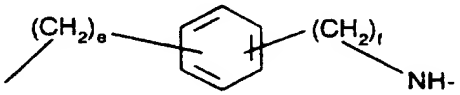
for the preparation of a pharmaceutical composition for the treatment of a retroviral disease in a warm-blooded animal which disease is responsive to the inhibition of the interaction of a transcriptional regulator with a retroviral response element.

2. The use according to claim I of a compound of formula I wherein

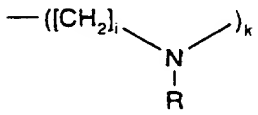
R_1 and R_2 are, independently of each other, a basic group selected from amino, N-alkyl-amino, N,N-dialkylamino, cycloalkylamino, amidino, N-lower alkylamidino, N,N-di-lower alkyl-amidino, guanidino, N-lower alkylguanidino and N,N-di-lower alkylguanidino,

X and Y are independently a bivalent radical of the formula $-(CH_2)_b-$

Z is a bivalent radical of the formula



or



, wherein R is hydrogen or lower alkyl, said bivalent radical being

bound via its $-(CH_2)_e-$ or $-(CH_2)_i-$ to the nitrogen and via its -NH- or -N(R)- to Q in formula I,

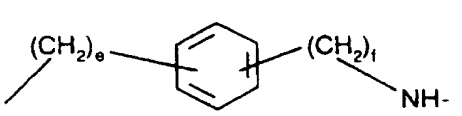
Q is selected from aryl, arylcarbonyl, arylaminocarbonyl, heterocyclyl, heterocyclylcarbonyl or heterocyclylaminocarbonyl, especially from heterocyclyl and heterocyclylcarbonyl; aryl or heterocyclyl whenever mentioned containing 2 or more annelated rings,

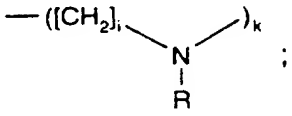
aryl comprising 2 or more annelated rings in the definitions of Q being selected from indenyl, indanyl, naphthyl, anthryl, phenanthryl, acenaphthyl or fluorenyl, which are unsubstituted or substituted by one or more substitutents selected from lower alkyl, halo-lower alkyl, phenyl, 1- or 2-naphthyl, oxo, hydroxy, lower alkoxy, carbamoyl-lower alkoxy, N-lower alkylcarbamoyl-lower alkoxy or N,N-di-lower alkylcarbamoyl-lower alkoxy, amino, mono- or di-lower alkylamino, lower alkanoylamino, halogen, carboxy, lower alkoxycarbonyl, phenyl-, naphthyl- or fluorenyl-lower alkoxycarbonyl, lower alkanoyl, sulfo, lower alkanesulfonyl, phosphono, hydroxy-lower alkoxyphosphoryl or di-lower alkoxyphosphoryl, carbamoyl, mono- or di-lower alkylcarbamoyl, sulfamoyl, mono- or di-lower alkylaminosulfonyl, nitro and cyano;

and heterocyclyl comprising 2 or more annelated rings being selected from indolyl, isoindolyl, 4,5,6,7-tetrahydro indolyl, indolizinyl, *3H*-indolyl, indazolyl, benzo-2-oxy-1,3-diazolyl, purinyl, benzimidazolyl, benzofuranyl, isobenzofuranyl, quinolyl, isoquinolyl, 1,2,3,4-tetrahydroquinolyl or 1,2,3,4-tetrahydroisoquinolyl, *4H*-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, cinnolinyl, pteridinyl, chromenyl, chromanyl, isochromanyl, cyclohexa[b]pyrrolyl, cyclohexa[b]pyridyl, cyclohexa[b]pyrazinyl, cyclohexa[b]pyrimidinyl, xanthenyl, phenoxythiinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, 2,3-dihydro-2-azaphenalenyl, perimidinyl, phenanthrolinyl, phenazolinyl, phenothiazinyl and phenoxazinyl, each of which is unsubstituted or substituted by one or more substituents selected from lower alkyl, phenyl, 1- or 2-naphthyl, phenyl-lower alkyl, hydroxy-lower alkyl, hydroxy, lower alkoxy, amino, lower alkylamino, di-lower alkylamino, carboxy, lower alkoxycarbonyl, phenyl- or naphthyl-lower alkoxycarbonyl, halogen, lower alkanoyl, nitro, oxo and cyano,

b is 2 to 7,
e and f is 1 to 3, respectively,
i is 2 to 7, and
k is 1,

with the proviso that Q is arylcarbonyl, arylaminocarbonyl, heterocyclylcarbonyl or heterocyclylaminocarbonyl only if Z is a bivalent radical of the formula



or


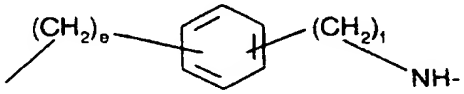
;

a tautomer thereof, or a salt thereof.

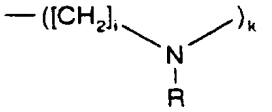
3. The use according to claim I of a compound of formula I wherein

R_1 and R_2 each are amino,

X and Y are independently a bivalent radical of the formula $-(CH_2)_b-$

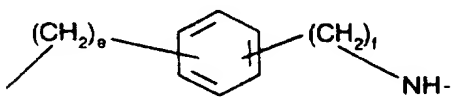
Z is, independently of X and Y, one of the residues mentioned in the definition of X and Y or is a bivalent radical of the formula


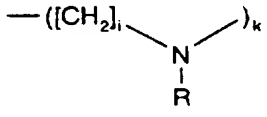
or



, wherein R is hydrogen, said bivalent radical being bound via its $-(CH_2)_e-$ or $-(CH_2)_i-$ to the nitrogen and via its -NH- or -N(R)- to Q in formula I,

Q is selected from purinyl, acridinyl, 1,8-naphthalimidyl or benzo-2-oxy-1,3-diazolyl, each of which is unsubstituted or substituted with one or more substituents selected from hydroxy, lower alkoxy, halogen and nitro; or, if Z is a bivalent radical of the formula



or


, Q is acridinylcarbonyl;

b is 2 to 7,

e and f is 1, respectively,

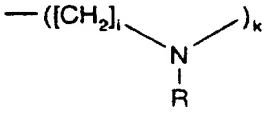
i is 2 to 7, and

k is 1,

a tautomer thereof, or a salt thereof.

4. The use according to claim I of compounds of formula I wherein
R_1 and R_2 each are amino,

X and Y are independently a bivalent radical of the formula $-(CH_2)_b-$,

Z is a bivalent radical of the formula  , wherein R is hydrogen, said bivalent radical being bound via its $-(CH_2)_i-$ to the nitrogen and via its -N(R)- to Q in formula I,

Q is selected from 6-chloro-2-methoxy-acridin-9-yl, and acridinylcarbonyl;

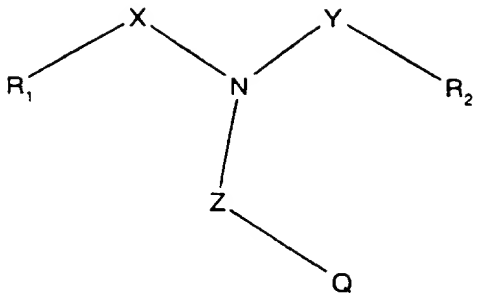
b is 2 to 7,
i is 2 to 4, and
k is 1,

or a salt thereof.

5. The use according to any one of claims 1 to 4 of a compound of formula I, a tautomer thereof or a salt thereof, in the preparation of a pharmaceutical composition for the treatment of HIV-infections which are responsive to the inhibition of the interaction between Tat and TAR and/or Rev and RRE.

6. The use according to any one of claims 1 to 4 of a compound of formula I, a tautomer thereof or a salt thereof, in the preparation of a pharmaceutical composition for the treatment of AIDS and its initial stages in humans by inhibition of the interaction between Tat and TAR and/or Rev and RRE of HIV-1

7. A compound of formula I



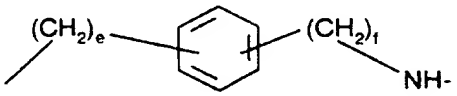
(I)

wherein

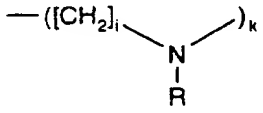
R_1 and R_2 are, independently of each other, a basic group selected from amino, N-alkylamino, N,N-dialkylamino, cycloalkylamino, amidino, N-lower alkylamidino, N,N-di-lower alkylamidino, guanidino, N-lower alkylguanidino and N,N-di-lower alkylguanidino;

X and Y are independently a bivalent radical of the formula $-(CH_2)_b-$,

Z is, independently of X and Y, one of the residues mentioned in the definition of X and Y or

is a bivalent radical of the formula 

or



, wherein R is hydrogen or lower alkyl, said bivalent radical being

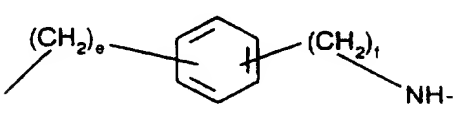
bound via its $-(CH_2)_e-$ or $-(CH_2)_i-$ to the nitrogen and via its -NH- or -N(R)- to Q in formula I,

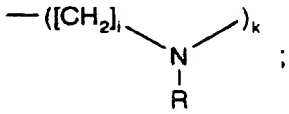
Q is selected from heterocyclyl and heterocyclylcarbonyl, heterocyclyl being selected from indolyl, isoindolyl, 4,5,6,7-tetrahydro indolyl, indolizinyl, *3H*-indolyl, indazolyl, benzo-2-oxy-1,3-diazolyl, purinyl, benzimidazolyl, benzofuranyl, isobenzofuranyl, isoquinolyl, 1,2,3,4-tetrahydroquinolyl or 1,2,3,4-tetrahydroisoquinolyl, *4H*-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, cinnolinyl, pteridinyl, chromenyl, chromanyl, isochromanyl, cyclohexa[b]pyrrolyl, cyclohexa[b]pyridyl, cyclohexa[b]pyrazinyl, cyclohexa[b]pyrimidinyl, xanthenyl, phenoxythiinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, 2,3-dihydro-2-azaphenalenyl, perimidinyl, phenanthrolinyl, phenazolinyl, phenothiazinyl and phenoxazinyl, each of which is unsubstituted or substituted by one or more substituents selected from lower alkyl, phenyl, 1- or 2-naphthyl, phenyl-lower alkyl, hydroxy-

lower alkyl, hydroxy, lower alkoxy, amino, lower alkylamino, di-lower alkylamino, carboxy, lower alkoxycarbonyl, phenyl- or naphthyl-lower alkoxycarbonyl, halogen, lower alkanoyl, nitro, oxo and cyano,

b is 2 to 7,
e and f is 1 to 3,
i is 2 to 7, and
k is 1,

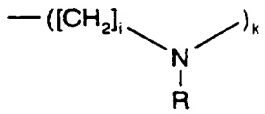
with the proviso that
(i) Q is heterocyclylcarbonyl only if Z is a bivalent radical of the formula



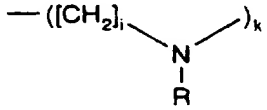
or


;

and with the further proviso that,

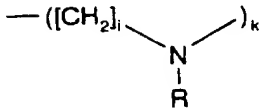
(ii) if each of R_1 and R_2 is amino, Z is a bivalent radical of the formula


, wherein R is hydrogen or lower alkyl, X and Y are $-(CH_2)_b-$ and Q is acridin-9-ylcarbonyl or 6-chloro-2-methoxy-acridin-9-yl, then at least in one of the residues X and Y b is 3 or larger,

with the further proviso that
(iii) a compound wherein each of R_1 and R_2 is amino, each of X and Y is $-(CH_2)_6-$, Z is a bivalent radical of the formula


bound as described above wherein i is 3, k is 1 and R is hydrogen, and Q is 6-chloro-2-methoxy-acridin-9-yl is excluded;

and with the further proviso that

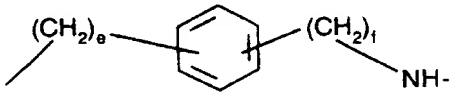
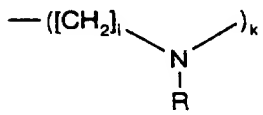
(iv) a compound wherein each of R_1 and R_2 is diethylamino, each of X and Y is $-(CH_2)_3-$, Z is a bivalent radical of the formula  bound as described above wherein i is 2, k is 1 and R is hydrogen, and Q is acridin-9-ylcarbonyl is excluded;

a tautomer thereof, or a salt thereof.

8. A compound of formula I according to claim 7, wherein

R_1 and R_2 are, independently of each other, a basic group selected from amino, N-alkylamino, N,N-dialkylamino, cycloalkylamino, amidino, N-lower alkylamidino, N,N-di-lower alkylamidino, guanidino, N-lower alkylguanidino and N,N-di-lower alkylguanidino

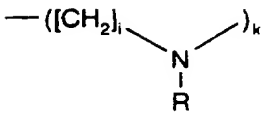
X and Y independently are a group of the formula $-(CH_2)_b-$,

Z is, independently of X and Y, one of the residues mentioned in the definition of X and Y or is a bivalent radical of the formula  or  , wherein R is hydrogen, said bivalent radical being bound via its $-(CH_2)_e-$ or $-(CH_2)_i-$ to the nitrogen and via its -NH- or -N(R)- to Q in formula I,

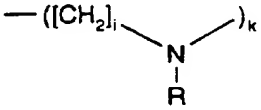
Q is selected from purinyl, acridinyl, 1,8-naphthalimidyl and benzo-2-oxy-1,3-diazolyl, each of which is unsubstituted or substituted with one or more substituents selected from hydroxy, lower alkoxy, halogen and nitro;
or is acridinylcarbonyl,

b is 2 to 6,
e and f is 1, respectively,
i is 2 to 4 and
k is 1,

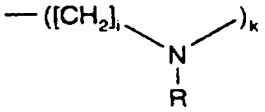
with the proviso that

(i) Q is acridinylcarbonyl only if Z is a bivalent radical of the formula  ;

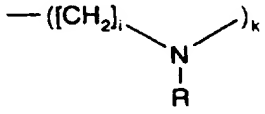
with the further proviso that,

(ii) if each of R_1 and R_2 is amino, Z is a bivalent radical of the formula  , wherein R is hydrogen, X and Y are $-(CH_2)_b-$ and Q is acridin-9-ylcarbonyl or 6-chloro-2-methoxy-acridin-9-yl, then at least in one of the residues X and Y b is 3 or larger,

with the further proviso that

(iii) a compound wherein each of R_1 and R_2 is amino, each of X and Y is $-(CH_2)_6-$, Z is a bivalent radical of the formula  bound as described above wherein i is 3, k is 1 and R is hydrogen, and Q is 6-chloro-2-methoxy-acridin-9-yl is excluded;

and with the further proviso that

(iv) a compound wherein each of R_1 and R_2 is diethylamino, each of X and Y is $-(CH_2)_3-$, Z is a bivalent radical of the formula  bound as described above wherein i is 2, k is 1 and R is hydrogen, and Q is acridin-9-ylcarbonyl is excluded;

a tautomer thereof, or a salt thereof.

9. A compound of formula I acording to claim 7 wherein

each of R_1 and R_2 is amino,

X and Y independently are a group $-(CH_2)_b-$,

Z is, independently of X and Y, $-(CH_2)_b-$,

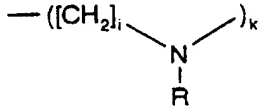
Q is selected from 1,8-naphthalimido which is unsubstituted or substituted with one or more substituents selected from hydroxy, lower alkoxy, halogen and nitro;

b is 2 to 6, and
e and f is 1, respectively,

or a salt thereof.

10. A compound of formula I according to claim 7, wherein
each of R_1 and R_2 is amino,

X and Y are independently a group $-(CH_2)_b-$,

Z is a bivalent radical of the formula  , wherein R is hydrogen, said bivalent radical being bound via its $-(CH_2)_i-$ to the nitrogen and via its -N(R)- to Q in formula I,

Q is selected from purinyl and benzo-2-oxy-1,3-diazolyl, each of which is unsubstituted or substituted with one or more substituents selected from hydroxy, lower alkoxy, halogen and nitro,
or is acridinyl;

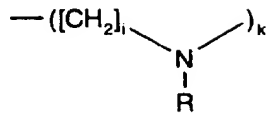
b is 2 to 6,
e and f is 1, respectively,
i is 2 to 4 and
k is 1,

or a salt thereof.

11. A compound of formula I according to claim 7, wherein

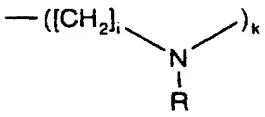
each of R_1 and R_2 is amino,

X and Y are independently a group $-(CH_2)_b-$,

Z is a bivalent radical of the formula  , wherein R is hydrogen, said bivalent radical being bound via its $-(CH_2)_i-$ to the nitrogen and via its -N(R)- to Q in formula I,

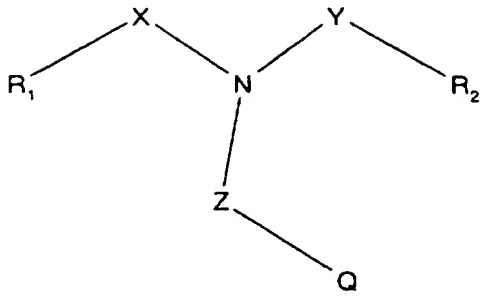
Q is acridinyl which is unsubstituted or substituted with one or more substituents selected from hydroxy, lower alkoxy, halogen and nitro,
or is acridinylcarbonyl, such as acridin-9-yl-carbonyl,

b is 3 to 6,
e and f is 1, respectively,
i is 2 to 4 and
k is 1,

with the proviso that
a compound wherein each of R_1 and R_2 is diethylamino, each of X and Y is $-(CH_2)_3-$, Z is a bivalent radical of the formula  bound as described above wherein i is 2, k is 1 and R is hydrogen, and Q is acridin-9-ylcarbonyl is excluded;

or a salt thereof.

12. A compound of formula I,



(I)

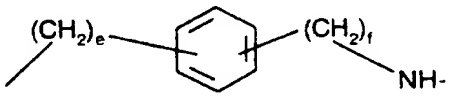
wherein

R_1 and R_2 are, independently of each other, a basic group selected from amino, N-alkylamino, N,N-dialkylamino, cycloalkylamino, amidino, N-lower alkylamidino, N,N-di-lower alkylamidino, guanidino, N-lower alkylguanidino and N,N-di-lower alkylguanidino,

X and Y are a bivalent radical independently selected from the group consisting of

$-(CH_2)_b-$, $-CH_2-(CH=CH-)_cCH_2-$, $-CH_2-(C\equiv C-)_dCH_2-$ and $-(CH_2)_g-$

Cycloalkylen-$(CH_2)_h-$,

Z is a bivalent radical of the formula 

, said bivalent

radical being bound via its $-(CH_2)_e-$ to the nitrogen and via its -NH- to Q in formula I,

Q is selected from heterocyclyl and heterocyclylcarbonyl, heterocyclyl being bound via a ring carbon atom and being selected from indolyl, isoindolyl, 4,5,6,7-tetrahydro indolyl, indolizinyl, *3H*-indolyl, indazolyl, benzo-2-oxy-1,3-diazolyl, purinyl, benzimidazolyl, benzofuranyl, isobenzofuranyl, quinolyl, isoquinolyl, 1,2,3,4-tetrahydroquinolyl or 1,2,3,4-tetrahydroisoquinolyl, *4H*-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, cinnolinyl, pteridinyl, chromenyl, chromanyl, isochromanyl, cyclohexa[b]pyrrolyl, cyclohexa[b]pyridyl, cyclohexa[b]pyrazinyl, cyclohexa[b]pyrimidinyl, xanthenyl, phenoxythiinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, 2,3-dihydro-2-azaphenalenyl, perimidinyl, phenanthrolinyl, phenazolinyl, phenothiazinyl and phenoxazinyl, each of which is unsubstituted or substituted by one or more substituents selected from lower alkyl, phenyl, 1- or 2-naphthyl, phenyl-lower alkyl, hydroxy-lower alkyl, hydroxy, lower alkoxy, amino, lower alkyl-

amino, di-lower alkylamino, carboxy, lower alkoxycarbonyl, phenyl- or naphthyl-lower alkoxycarbonyl, halogen, lower alkanoyl, nitro, oxo and cyano,

b is 2 to 7,
c, d, e and f are 1 to 3, respectively, and
g and h are 0 to 3, respectively,

a tautomer thereof, or a salt thereof.

13. A compound of formula I, selected from the compounds named
5-(3-{6-chloro-2-methoxy-acridin-9-yl}-aminopropyl)-1,5,10-triazadecane,
5-(2-{4-acridinoyl}-aminoethyl)-1,5,10-triazadecane,
N-(3-[1,5,10-triazadecan-5-yl]-propyl)-3-nitro-1,8-naphthalimide,
N-(2-[1,5,10-triazadecan-5-yl]-ethyl)-1,8-naphthalimide,
N-(3-[1,5,10-triazadecan-5-yl]-propyl)-4-chloro-1,8-naphthalimide,
N-(2-[1,5,10-triazadecan-5-yl]-ethyl)-3-hydroxy-1,8-naphthalimide,
5-(3-{6-chloro-2-methoxy-acridin-9-yl}-aminopropyl)-1,5,9-triazanonane,
6-(3-{6-chloro-2-methoxy-acridin-9-yl}-aminopropyl)-1,6,11-triazaundecane,
5-(4-{6-chloro-2-methoxy-acridin-9-yl}-aminobutyl)-1,5,10-triazadecane and
5-(2-{6-chloro-2-methoxy-acridin-9-yl}-aminoethyl)-1,5,10-triazadecane,
or a pharmaceutically acceptable salt thereof.

14. A compound of formula I according to claim 7, selected from 5-(5-{6-chloro-2-methoxy-acridin-9-yl}-aminopentyl)-1,5,10-triazadecane and
6-(4-{6-chloro-2-methoxy-acridin-9-yl}-aminopentyl)-1,6,11-triazaundecane,
or a pharmaceutically acceptable salt thereof, respectively

15. A compound of formula I, a salt thereof or a tautomer thereof according to any one of claims 7 and 12 for use in the treatment of a retroviral disease in a warm-blooded animal which disease is responsive to the inhibition of the interaction of transcriptional regulators with retroviral response elements.

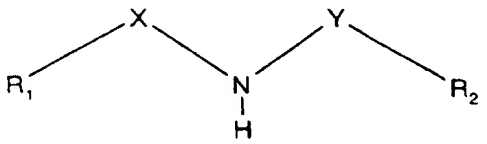
16. A pharmaceutical composition for the treatment of a retroviral disease in a warm-blooded animal which disease is responsive to the inhibition of the interaction of transcrip-

tional regulators with retroviral response elements, said composition comprising a compound of formula I according to claim 7 or claim 12 and a pharmaceutically acceptable carrier material.

17. A method of treating a retroviral infection by inhibiting the interaction of a transcriptional regulator with a retroviral response element, which comprises administering a therapeutically effective amount of a compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, to a warm-blooded animal, who on account of at least one of the mentioned diseases requires such treatment.

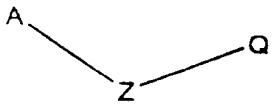
18. A process for the manufacture of a compound of formula I according to any one of claims 7 and 12, said process comprising

a) reacting an imino compound of the formula II



(II)

wherein R_1, R_2, X and Y are defined as for compounds of formula I, with a compound of formula III,



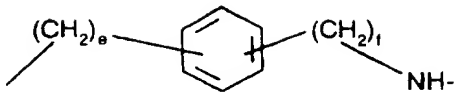
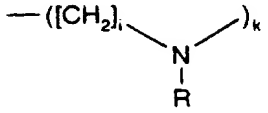
(III)

wherein

Z and Q are as defined for compounds of formula I and

A is a nucleofugal leaving group, the starting materials where necessary being present in protected form, and removing any protecting groups being present; or

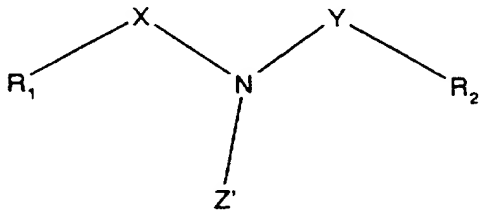
b) for the synthesis of a compound of formula I

wherein Z is a bivalent moiety of the formula  or of the formula  , wherein R, e, f, i and k are as defined for compounds of formula I,

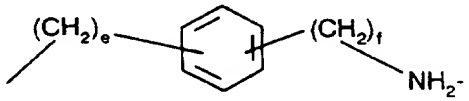
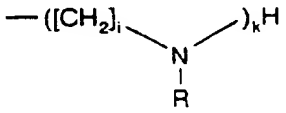
Q is aryl, arylcarbonyl, heterocyclyl that is not bound via a ring nitrogen atom or heterocyclylcarbonyl

and e, f, i, k, R_1, R_2, X and Y are as defined for compounds of formula I,

reacting an amino compound of the formula IV,

 (IV)

wherein R_1, R_2, X and Y are as defined for compounds of formula I and

Z' is  or 

wherein R, e, f, i and k are as defined for compounds of formula I,

with a compound of formula V,

Q-L (V)

wherein

Q is aryl, arylcarbonyl, heterocyclyl that is not bound via a ring nitrogen atom or heterocyclylcarbonyl and

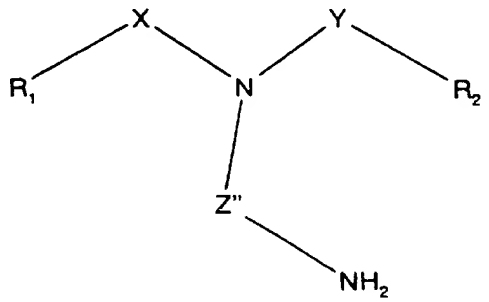
L is a leaving group,

the starting materials where necessary being present in protected form, and removing any protecting groups being present; or

c) for the synthesis of a compound of formula I wherein

Z is $-(CH_2)_b-$, wherein b is as defined for a compound of formula I,
Q is unsubstituted or substituted 1,8-naphthalimido and
R_1, R_2, X, Y and b are as defined for a compound of formula I,

reacting an amino compound of the formula VI,



(VI)

wherein
Z" is $-(CH_2)_b-$, and
R_1, R_2, X and Y are as defined for a compound of formula I,

with unsubstituted or substituted 1,8-naphthalene-dicarboxylic acid or a reactive derivative thereof,
the starting materials where necessary being present in protected form, and removing any protecting groups being present;

and, if desired, transforming a compound of formula I into a different compound of formula I, transforming a salt of an obtainable compound of formula I into the free compound or a different salt or an obtainable free compound of formula I into a salt, and/or separating obtainable mixtures of isomers of compounds of formula I into the individual isomers.

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(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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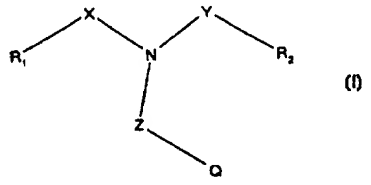
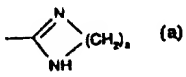
(54) Title: ANTIRETROVIRAL BASES

(57) Abstract

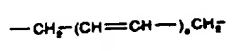
The invention relates to the use of a compound of formula (I), wherein R_1 and R_2 are independently amino, N-alkylamino, N,N-dialkylamino, cycloalkylamino, amidino, N-lower alkylamidino, N,N-di-lower alkylamidino, guanidino, N-lower alkylguanidino, N,N-di-lower alkylguanidino or (a); X and Y are independently selected from the group consisting of $-(CH_2)_b-$, (b), (c) and $-(CH_2)_g$-Cycloalkylen-$(CH_2)_h-$; Z is, independently of X and Y, $-(CH_2)_b-$, (d) or (e), wherein R is hydrogen or lower alkyl; Q is aryl, arylcarbonyl, arylaminocarbonyl, heterocyclyl, heterocyclylcarbonyl or heterocyclylaminocarbonyl, aryl or heterocyclyl whenever mentioned containing 2 or more annelated rings, a is 2 to 4, b is 2-7, c, d, e and f is 1 to 3, respectively, g and h is 0 to 3, respectively, i is 2 to 7 and k is 1 to 3, with the proviso that Q is arylcarbonyl, arylaminocarbonyl, heterocyclylcarbonyl or heterocyclylaminocarbonyl only if Z is a bivalent radical of formula (f) or (g); a tautomer thereof, or a salt thereof, as antiretroviral therapeutic (also for prophylaxis) inhibiting the interaction of transcriptional regulators with retroviral response elements.



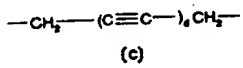
(I)



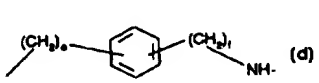
(a)



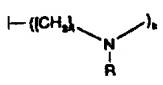
(b)



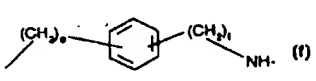
(c)



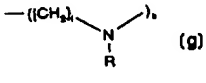
(d)



(e)



(f)



(g)

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/00139

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D219/12 A61K31/435 C07D219/04 C07D221/14 C07D473/40
C07D271/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	DATABASE WPI Section Ch, Week 8941 Derwent Publications Ltd., London, GB; Class B02, AN 89-297822 XP002030783 & JP 01 221 364 A (ZH BISEIBUTSU KAGAKU KEN) , 4 September 1989 see abstract --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 1997	24. 11. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Steendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	CHEMICAL ABSTRACTS, vol. 111, no. 9, 28 August 1989 Columbus, Ohio, US; abstract no. 070316, ATSUMI S ET AL: "Inhibition of human immunodeficiency virus-associated reverse transcriptase by aminoacridines" XP002030780 see abstract & DRUGS EXP. CLIN. RES. (DECRDP,03786501);88; VOL.14 (12); PP.719-22, INST. MICROB. CHEM.;TOKYO; 141; JAPAN (JP), ---	1-18
X	CHEMICAL ABSTRACTS, vol. 99, no. 7, 15 August 1983 Columbus, Ohio, US; abstract no. 53571n, HANSEN ET AL.: "A novel synthesis of tri-, di- and mono-9-acridinyl ..." XP002030781 &J.Chem.Soc.,Chem. Commun. 1983,(4),162-164 see abstract ---	7-16,18
X	CHEMICAL ABSTRACTS, vol. 122, no. 15, 10 April 1995 Columbus, Ohio, US; abstract no. 181808a, SHINOZUKA ET AL.: "Synthesis and RNA cleaving ..." XP002030782 & Nucleic Acids Symp. Ser. 1994, 31(21st Smposium on Nucleic Acids Chemistry, 1994), 167-168 see abstract ---	7-16,18
X	WO 95 11238 A (SMITHKLINE BEECHAM PLC ;COOPER DAVID GWYN (GB); KING RONALD JOSEPH) 27 April 1995 see the whole document ---	7-16,18
X	J.MED.CHEM., vol. 38, 1995, pages 1493-1504, XP002037237 CLARK ET AL.: "Antitumor imidazotetrazines..." see page 1494, compounds 28, 29 ---	7-16,18
X	DE 39 31 052 A (HOECHST AG) 22 March 1990 see page 2-3, formula (I), page 12, compound 17 ---	7-16,18

-/--

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 120, no. 9, 28 February 1994 Columbus, Ohio, US; abstract no. 101125w, SHINOZUKA ET AL.: "Non-radioisotope labeling of DNA ..." XP002037238 & Nucleic Acids Symp. Ser. 1993, 29, 73-74 (RN 151921-85-6) see abstract	7-16,18
X	CHEMICAL ABSTRACTS, vol. 121, no. 1, 4 July 1994 Columbus, Ohio, US; abstract no. 2054m, SHINOZUKA ET AL.: "Bi-functional labeling of DNA with ..." XP002037239 & Bioorg. Med. Chem. Lett., 1993, 3(12), 2883-2886 (RN 155303-18-7 see abstract	7-16,18
X	CHEMICAL ABSTRACTS, vol. 121, no. 9, 29 August 1994 Columbus, Ohio, US; abstract no. 99243h, IHARA ET AL.: "DNA intercalators bearing metal chelating ..." XP002037240 & Chem. Lett. 1994, (6), 1053-1056 (RN 156338-97-5) see abstract	7-16,18
X	CHEMICAL ABSTRACTS, vol. 111, no. 24, 11 December 1989 Columbus, Ohio, US; abstract no. 221377r, HUSTON ET AL.: "Chelation enhanced fluorescence detection ..." XP002037241 & J. Am. Chem. Soc. 1989, 111(23), 8735-8757) (RN 123623-03-0) see abstract	7-16,18
Y	WO 91 09850 A (KNOLL AG) 11 July 1991 see claim 4	1-18

INTERNATIONAL SEARCH REPORT

Int tional application No.
PCT/EP 97/00139

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims 1-18 partially
2. Claims 1-18 partially

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by ...e applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/EP 97/00139

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